

CA20N
Z 1
-83H021

3 1761 11850005 7



8

**ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND
RELATED MATTERS.**

Hearing held in Court Room 20
Court House
361 University Avenue
Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange	Commissioner
P.S.A. Lamek, Q.C.	Counsel
E.A. Cronk	Associate Counsel
Thomas Millar	Administrator

Transcript of evidence
for

July 6th, 1983

VOLUME 8

OFFICIAL COURT REPORTERS

Angus, Stonehouse & Co. Ltd.,
14 Carlton Street, 7th Floor,
Toronto, Ontario M5B 1J2

595-1065



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

1 ROYAL COMMISSION OF INQUIRY INTO CERTAIN
2 DEATHS AT THE HOSPITAL FOR SICK CHILDREN
AND RELATED MATTERS.

3

4

Hearing held in Court Room 20,
5 Court House, 361 University
Avenue, Toronto, Ontario, on
6 Wednesday the 6th day of July,
1983.

7

8

9

10 THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
11 THOMAS MILLAR - Administrator
12 MURRAY R. ELLIOT - Registrar

13

14

15 APPEARANCES:

16	E.A. CRONK	Commission Counsel
17	D. HUNT) L. CECCHETTO)	Counsel for the Attorney- General and Solicitor General of Ontario (Crown Attorneys and Coroner's Office)
18	I.G. SCOTT, Q.C.) I.J. ROLAND) R. DEVINS) R. BATTY)	Counsel for The Hospital for Sick Children
19	D. YOUNG	Counsel for The Metropolitan Toronto Police
20	K. CHOWN	Counsel for numerous Doctors at The Hospital for Sick Children
21	F. KITELY	Counsel for the Registered Nurses' Association of Ontario and 35 Registered Nurses at The Hospital for Sick Children

(Cont'd)



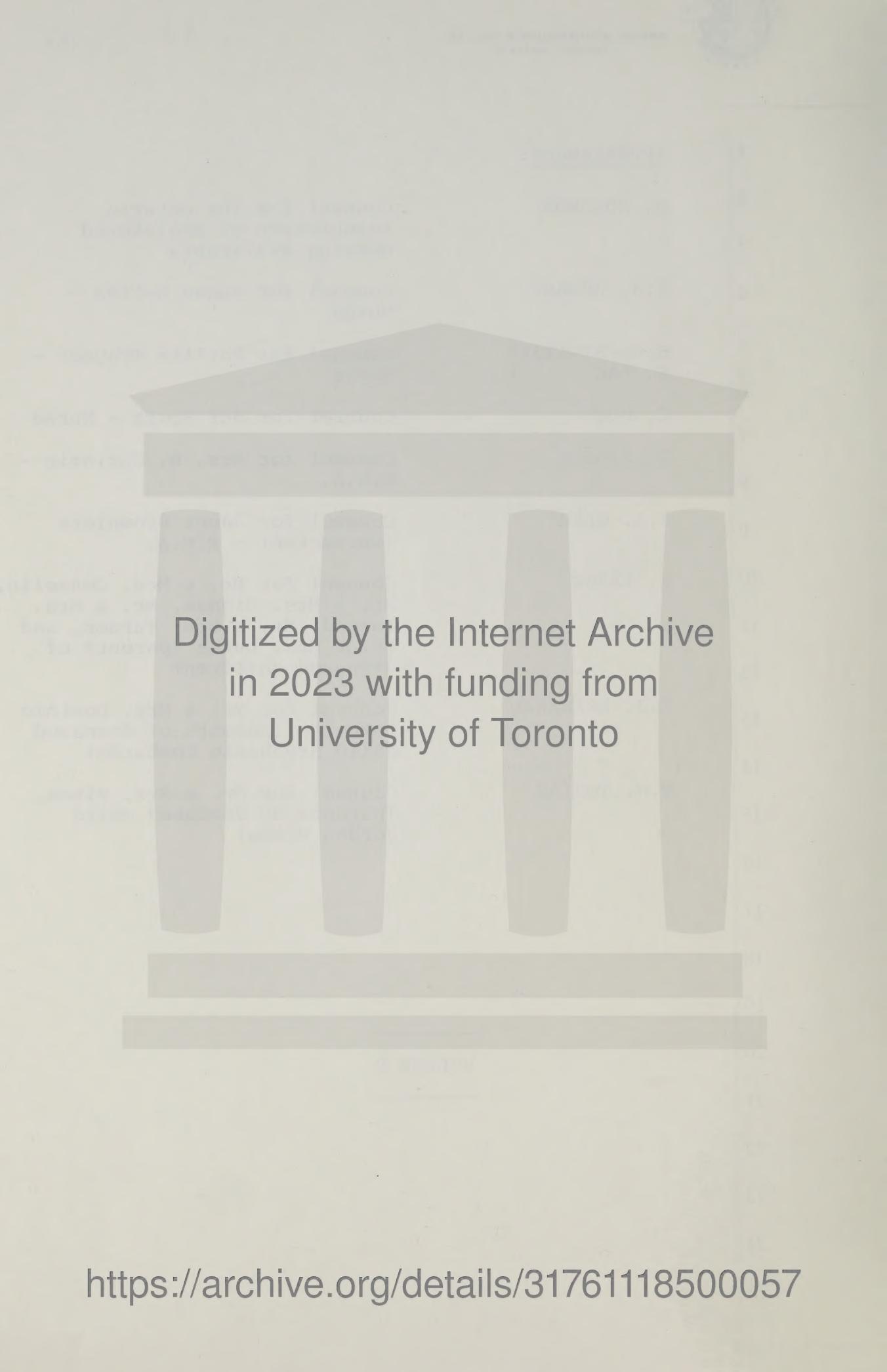
ANGUS, STONEHOUSE & CO., LTD.
TORONTO, ONTARIO

(b)

APPEARANCES:

- | | | |
|----|---------------|---|
| 2 | H. SOLOMON | Counsel for the Ontario
Association of Registered
Nursing Assistants |
| 4 | W.A. BOGART | Counsel for Susan Nelles -
Nurse |
| 5 | G.R. STRATHY) | Counsel for Phyllis Trayner - |
| 6 | P. RAE) | Nurse |
| 7 | C. BUHR | Counsel for Sui Scott - Nurse |
| 8 | B. KNAZAN | Counsel for Mrs. M. Christie -
R.N.A. |
| 9 | J.A. OLAH | Counsel for Janet Brownless
(Vereecken) - R.N.A. |
| 10 | S. LABOW | Counsel for Mr. & Mrs. Gosselin,
Mr. & Mrs. Gionas, Mr. & Mrs.
Inwood, Mr. & Mrs. Turner, and
Mr. & Mrs. Lutes (parents of
deceased children) |
| 13 | F.J. SHANAHAN | Counsel for Mr. & Mrs. Dominic
Lombardo (parents of deceased
child Stephanie Lombardo) |
| 15 | W.W. TOBIAS | Counsel for Mr. & Mrs. Hines,
(parents of deceased child
Jordan Hines) |

VOLUME 8



Digitized by the Internet Archive
in 2023 with funding from
University of Toronto

<https://archive.org/details/31761118500057>



1 INDEX OF WITNESSES

2	NAME	Page No.
4	<u>ELLIS</u> , Graham (Dr.) Resumed	1203
5	Examination by Mr. Scott	1204
	Re-Examination by Ms. Cronk	1207
6	<u>SOLDIN</u> , Steven (Dr.) Sworn	1234
7	<i>Re-</i> Direct Examination by Ms. Cronk	1234

14 INDEX OF EXHIBITS

15	No.	Description	Page No.
16	19	Article entitled "Myocardial vs Serum Digoxin Concentrations in Infants and Adults".	1208
18	20	Article entitled "Correlation of Antemortem and Postmortem Digoxin Levels".	1209
20	21	Article entitled "Post-Mortem Digoxin Levles Two Unusual Case Reports" by S.J. Dickson and N.D. Blazey.	1210
22	22	Copy of Chart produced by Ms. Cronk.	1211
23	23	Curriculum Vitae of Dr. Steven John Soldin.	1239



1 INDEX OF EXHIBITS (Cont'd)

2	No.	Description	Page No.
3	24	Document entitled "Cardiac Glycoside Drug Assays - TDX Digoxin".	1313
5	25	Memo from Dr. Soldin to Dr. MacLeod dated June 15th, 1983 re Digoxin Measurements.	1357
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

1203

A/DP/ak

1

2

---Upon commencing at 10:00 a.m.

3

DR. GRAHAM ELLIS, Resumed

4

THE COMMISSIONER: Mr. Buhr, have
I called on you?

6

MR. BUHR: I have no questions,
Mr. Commissioner.

7

THE COMMISSIONER: Is there anyone
here for Mrs. Christie?

9

MS. GOODMAN: No questions.

10

THE COMMISSIONER: Mr. Young, do
you have any questions?

12

MR. YOUNG: I do not have any

questions, Mr. Commissioner.

13

THE COMMISSIONER: Miss Chown?

15

MS. CHOWN: No questions.

16

THE COMMISSIONER: We are doing
well, are we not? I think I should start at
about a quarter to 10:00 and then I will really get
through this. Mr. Roland?

19

MR. ROLAND: I hate to disappoint
you, Mr. Commissioner, but I have no questions
either, sir.

22

THE COMMISSIONER: All right.

23

Mr. Labow?

24

25

MR. LABOW: I have no questions and



1

2

3

Mr. Shanahan also informed me that he would not have any questions.

4

5

THE COMMISSIONER: All right. We are doing well. Mr. Scott?

6

EXAMINATION BY MR. SCOTT:

7

Q. Dr. Ellis, I would just like to ask you one or two questions in two areas.

8

9

10

First of all, Mr. Strathy yesterday asked you some questions about the testing you do and the record books you maintain of those tests.

11

Do you recall that?

12

A. Yes.

13

14

15

16

17

18

19

Q. And in that connection he asked you if you were able to determine from an examination of your books the number of tests that would have been at the toxic level, which is the way he put it. Do you remember that? He asked you, following that, if you could at some time give to the Inquiry the percentage of tests, over a given period, at the toxic level. Do you remember that?

20

21

A. Yes, I think that was one of his questions, but I thought he had backed off from that.

22

23

Q. Well, just to be sure he backed off, we are going to deal with it. I take it that

24

25



1

2

the toxic level is the level above the therapeutic
level?

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. I don't know quite how he defined it. I indicated that I had searched those books on a previous occasion for levels greater than 5 and had presented a list to the Preliminary Hearing.

Q. Let me put this to you. The

so-called therapeutic level of digoxin, that level, I take it, is determined arbitrarily by a literature search?

A. Yes.

Q. And a level above that

therapeutic level is what is sometimes called the toxic level?

A. Yes.

Q. Am I right?

A. Yes.

Q. Simply because it is above a certain ---

A. Threshold level.

Q. Threshold level. Now, I take it that you as a chemist have no capacity to determine whether any level is in fact toxic?

A. On the clinical indications that



1

2

the patient may be showing at that particular time,
I have no knowledge of those clinical symptoms.

4

5

6

Q. Would it be correct to say
that whether a digoxin level is in fact toxic is
something that is not for your expertise?

7

A. Yes.

8

Q. It is for the expertise of the
clinician on the spot?

9

A. Yes.

10

11

12

13

14

15

Q. Now, Mr. Hunt asked you some
questions about the differences between your disci-
pline and the discipline of a forensic chemist. I
do not intend to get into that interesting question
but I simply want to ask you this. You heard
Mr. Cimbura's evidence?

16

17

A. Yes.

Q. And you heard him describe

18

RIA testing for digoxin, did you?

19

A. Yes.

20

21

22

Q. Was there anything in the RIA
testing for digoxin that he described that was
foreign to your expertise in terms of either theory
or practice?

23

A. Nothing that immediately comes

24

to mind.

25



1

2 Q. Is the RIA testing for digoxin
3 that he was doing parallel to the RIA testing for
4 digoxin that you traditionally do in the Hospital
5 for Sick Children?

6

A. Similar in many ways, yes.

7

MR. SCOTT: Those are all the
questions I have, thank you, Dr. Ellis.

8

9 MS. CRONK: Mr. Commissioner, we
10 were supplied last night with a copy of the articles
11 which, as I understand it, Dr. Ellis referred to
12 during the course of cross-examination by Miss Symes
13 yesterday and I propose that they be marked now as
14 exhibits.

15

16 Perhaps, Dr. Ellis, just to ensure
17 that I do have the right articles you can let me
know if I refer to any that you did not refer to,
but it is my understanding that these are the three
18 that you referred to with Miss Symes.

19

20 The first, Mr. Commissioner, is
21 entitled "Myocardial vs Serum Digoxin Concentrations
22 in Infants and Adults", published in May 1982,
23 co-authored by Park, Ludden and others.

24

RE-EXAMINATION BY MS. CRONK:

25

Q. Is that one of the articles to
which you referred, Dr. Ellis?



1

2

A. Was that the third article to
which I referred?

4

THE COMMISSIONER: Where was it

5 published?

6

7 MS. CRONK: Q. Would you look at that
article, Dr. Ellis, and just let us know where that
8 was published and if that was one of the ones that
you referred to?

9

10 A. Yes, the "Myocardial vs Serum
Digoxin Concentrations...?"

11

Q. Yes.

12

13 A. The American Journal of
Diseases in Children or Childhood - I think it is
14 Children - Volume 136, May, 1982.

15

Q. Thank you.

16

17 Could that be marked then,
Mr. Commissioner, as the next exhibit, please.

18

19 THE COMMISSIONER: Exhibit 19.

20

21 ---EXHIBIT NO. 19: Article entitled "Myocardial
22 vs Serum Digoxin Concentrations
23 in Infants and Adults".

24

25 MS. CRONK: Q. And the next one
that I have before me is entitled "Correlation of
Antemortem and Postmortem Digoxin Levels".

26

27 Do you have that before you?

28

29



1

2

A. Yes.

3

4

Q. Can you tell the Commissioner
by whom it was published, when and where?

5

6

7

8

A. This was in the Journal of
Forensic Science, Volume 23, page 329 to 334, 1978.
The authors are V-o-r-p-a-h-l, T. E., (I do not know
how it is pronounced) and Coe, C-o-e, J. I.

9

10

MS. CRONK: Could that be marked,
sir, as the next exhibit, please?

11

THE COMMISSIONER: Exhibit 20.

12

13

---EXHIBIT NO. 20: Article entitled "Correlation
of Antemortem and Postmortem
Digoxin Levels".

14

15

16

MS. CRONK: Q. The third article
that I have, Dr. Ellis, is entitled "Post-Mortem
Digoxin Levels-Two Unusual Case Reports".

17

18

Could you tell the Commissioner
again who the authors of that report were and where
it was published and when?

19

20

21

22

A. Yes, the authors are Dickson,
S.J. and Blazey, B-l-a-z-e-y, N.D. And this was
in the Forensic Science, Volume 9, 1977, page 145
to 150.

23

24

25

Q.. Thank you.

Again, sir, could that be marked as



1

2

the next exhibit?

3

THE COMMISSIONER: Exhibit 21.

4

5

---EXHIBIT NO. 21: Article entitled "Post-Mortem
Digoxin Levels-Two Unusual
Case Reports" by S.J. Dickson
and N.D. Blazey.

6

7

MR. ROLAND: Excuse me,

8

9

Mr. Commissioner, could you advise us what exhibit
numbers these are?

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

THE COMMISSIONER: Yes, 19, 20 and
21 respectively.

MS. CRONK: One other question,

Mr. Commissioner, with respect to the last article
that we have just marked.

Q. Dr. Ellis, there is some hand-
writing that appears on the face page and throughout
the copy of the article that I have. Can you identify
that handwriting for us?

A. I did mark quite a few of
these articles. I think it is probably mine.

Q. Thank you.

The last exhibit, Mr. Commissioner,
at Mr. Strathy's request I have copies made of a
reduced version of this chart, and if it will be
of any utility to anyone in reviewing the transcript
I propose that it be marked as the next exhibit.



1

2

THE COMMISSIONER: Exhibit 22.

3

4

---EXHIBIT NO. 22: Copy of Chart produced by
Ms. Cronk.

5

MS. CRONK: Thank you.

6

Q. Dr. Ellis, just a few questions
if I may. You will recall that yesterday during
the cross-examination conducted by Ms. Symes your
attention was drawn to Exhibit 14 which, as you may
recall, is the publication produced by Antibodies Inc.
of California concerning its antiserum, the one that
is used by you in the hospital to conduct RIA
digoxin assays. Do you recall that?

13

A. Yes.

14

Q. It was suggested to you, and
as I understood your response to the questions put
to you by Ms. Symes, that the digoxin antiserum
produced by Antibodies Inc. and as referred to in
that publication was designed for ante mortem
sampling for digoxin. Do I have that correctly?

19

20

A. I believe that to be the case.

21

22

23

24

25



6 jul 83
B
BMcra

1

Q. All right.

2

A. Is there any indication other-
wise here?

3

Q. Well, I'll come to that in a
moment, Dr. Ellis. I just want to be clear as to
what I understood your evidence to be yesterday.

4

Do you recall Miss Symes asking you
and directing questions to you as to what the purpose
and design intent was of that antibody?

5

A. Yes.

6

Q. Do you recall that?

7

A. Yes.

8

Q. And as I recall your answers
to those questions, you indicated that they were
designed for ante mortem digoxin sample.

9

A. Yes.

10

Q. All right. Now, can you tell
me, Dr. Ellis, specifically the point that you now
raise, in any of the literature or promotional
materials that have ever been provided to you by
Antibodies Inc. with respect to that antiserum or,
indeed, any of the conversations that you've had
with the Quality Control Manager of that company
or others associated with the company, was any
indication given to you to suggest or to indicate

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25



Ellis
re.ex. (Cronk)

1

B2 2 that the antiserum was not suitable for post mortem
3 testing on plasma or serum samples?

4 A. No.

5 Q. Thank you.

6 And as I understood your evidence
7 yesterday as well, Dr. Ellis, you told Miss Symes
8 that, in your view, it would take several months to
9 adapt a method at the Hospital to conduct post
mortem testing on certain kinds of samples.

10 Do you recall that evidence?

11 A. Yes. I think it may well take
12 several months.

13 Q. All right.

14 I would like to be clear, and I may
15 well have heard it correctly yesterday, Dr. Ellis,
16 but I would like to be clear in my own mind, were
17 you drawing a distinction, in answering that
18 question, between particular types of samples or
19 were you referring to samples at large?

20 A. I think we have plenty of
21 experience in analyzing regular serum samples, but
22 it is just the other samples, other than those, that
23 would require some work to be done, I feel.

24 Q. Well, all right. More
25 specifically, can you help me with this: In your



Ellis
re.ex. (Cronk)

1

B3 2 view, would it take a period of several months to
3 adapt the RIA method that is being used in the
4 Hospital to test post mortem tissue samples?

5 A. I think it could well take
6 several months, yes.

7 Q. And similarly, to conduct
8 post mortem digoxin assays on serum samples, would
9 that also take several months to adapt your method?

10 A. Well, it could be used for
11 post mortem serum samples.

12 Q. As it stands today?

13 A. Just in the same way that
14 regular serum samples are used.

15 Q. All right.

16 A. And what is the situation with
17 respect to plasma samples?

18 A. But the interpretation may be
19 slightly different in the results you obtain.

20 Q. I appreciate that, Dr. Ellis,
21 but in terms of the technical capacity of the methodology
22 as it now exists in the Hospital to do post
23 mortem digoxen assays on serum samples, is that
24 something that could be done today without modifying
25 the system?

A. Well, that is something that we



B4

1

2 have been requested to do, and are doing currently
3 without a modified system.

4

Q. Thank you.

5

And similarly, what is the situation
5 with respect to plasma samples?

6

A. Plasma and serum, I would
7 equate those two.

8

Q. All right. So, am I correct,
9 then, that, in your view, no modification of the
10 methodology was necessary at the Hospital to conduct
11 post mortem tests on those two kinds of samples?

12

A. We undertook no studies when
13 we were requested to analyze post mortem serum
14 samples because of the similarity in many respects
15 between pre and post mortem serum samples. We did
16 think, I think, when we initially agreed to do these,
17 that it would be for a very short time only. We
18 hadn't really anticipated that we would still be
analyzing these samples.

19

Q. As you sit here today, you are
still doing that; is that correct?

20

A. We are doing that, yes. Yes.

21

Q. And you keep referring, Dr.
22 Ellis, to serum. Are you, in that context, using
23 serum interchangeably with plasma?

24

25



B5

1

2

A. Yes.

3

Q. Thank you.

4

In your judgment, Dr. Ellis, having regard to your experience in conducting radioimmunoassays for digoxin, do you have any misgivings in using the methodology or technique as it has been developed in the Hospital for the purpose of conducting post mortem digoxin assays on blood or serum samples?

10

A. On blood or serum --

11

Q. Yes.

12

A. -- or on plasma and serum?

13

Q. I'm sorry, plasma and serum; you're quite right.

14

A. Do I have any major misgivings in what respect?

16

Q. Well --

17

A. In respect of interpretation of the numbers that would be produced?

19

Q. Well, let's be clear about this.

20

As I understood it, the burden of your evidence before the Commissioner has been that it is not part of your function to interpret the results that come off of a particular assay reading; is that correct?

24

25



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Ellis
re.ex. (Cronk)

1217

B6

1

2

3

4

THE COMMISSIONER: I think you are

concerned about -- I think your question is the analysis, the result.

5

MS. CRONK: That's right.

6

7

Well, let me rephrase the question then, Mr. Commissioner. I apologize if it has been confusing, Dr. Ellis.

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Based on your experience as a biochemist in conducting radioimmunoassays, digoxin assays, in the Hospital, do you have any misgivings, as a biochemist, in terms of the technical capability of the methodology that is now in place in the Hospital for the purposes of running digoxin assays on post mortem serum or plasma samples?

A. No major misgivings, no, in that the protein composition of the pre and post mortem samples is essentially similar. The electrolyte composition is essentially similar.

Q. And I take it, sir - and perhaps you can tell me, would you have any misgivings about using the system to conduct a post mortem tissue --

A. Major misgivings, yes.

Q. Major misgivings, thank you.



Ellis
re.ex. (Cronk)

B7

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

And you told Mr. Strathy, as I recall it, that, in order to moderate the radioimmunoassay technique presently available in the Hospital for the purposes of conducting post mortem digoxin assays on tissue samples, that would require an addition to the modification of the system itself and, in your view, it would also require an extensive literature review; is that correct?

A. Yes, very much so.

Q. And I believe, if I understood your evidence correctly, that you also told him that you, if you were asked or required to modify the system for that purpose, would wish to speak to those persons whom you knew had experience in doing digoxin assays on tissue samples; is that correct?

A. That may cut down some of the time involved to do that, yes.

Q. Would that, in your view, be a desirable step to take if you were modifying your system for that purpose?

A. Yes.

Q. And in that context, would you consider it appropriate to discuss with Mr. Cimbura his experience in conducting those kinds of tests?



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

1219

Ellis
re.ex. (Cronk)

1

A. Yes, I think it would, Mr.

2 Cimbura or other people, too.

3 Q. And I believe, again if I
4 understood your evidence correctly, that you also
5 told Mr. Tobias, in his cross-examination of you
6 yesterday, that, in order to use the materials
7 supplied by Antibodies Inc., the antiserum for those
8 kinds of post mortem tests, the kit would have to
9 be used with - and at least this is what my note
10 of your evidence indicates - a lot of caution and a
11 lot of tests.

12 Do you recall giving that evidence?

13 A. A lot of caution, yes.

14 Q. Yes. All right.

15 A. And, again in that regard, were you
16 referring to particular kinds of samples that would
17 be tested on a post mortem basis or were you refer-
18 ring to samples at large?

19 A. Samples in general, in view
20 of the fact that tissues might have binding sub-
21 stances present that might interfere with the
22 simple radioimmunoassay.

23 Q. Were you referring as well to
24 plasma or serum samples?

25 A. I think it would depend. You're



1

2 talking about post mortem plasma?

3 Q. Yes, I am.

4 A. Yes. Well, it is difficult
5 to generalize, really, because if a child dies and
6 a blood sample is taken ten minutes after death from
7 an arm, then that sample is a post mortem sample
essentially.

8 Q. Yes.

9 A. But it is really very close to
10 the time when the patient was alive.

11 If, on the other hand, you go to
12 perhaps 24 hours afterwards, when an autopsy has
13 been performed, then you are in a kind of different
situation.

14 Q. In your view, doctor, then,
15 if you were to conduct or modify your system for
16 post mortem digoxin assays on plasma or serum, would
17 it require that you exercise the same degree of
18 caution and the same degree of multiple tests as
19 you suggested it would to use the Antibodies Inc.
20 antiserum for tissues?

21 A. I think so, because there may
22 be, particularly if the blood sample is taken from
23 the heart, there might perhaps have been some de-
composition, a partial decomposition of the heart

24

25



1

B10 2 tissue.

3 Q. Yes.

4 A. And this might perhaps have
5 released certain proteins from the heart tissue that
6 might possibly interfere with the assay.

7 All these things would have to be
8 tested for.

9 Q. All right.

10 A. And again, dealing now for the moment
11 with just post mortem testing on tissue samples, as
12 I understood your responses to Mr. Tobias, you
13 indicated, again in modifying the system, that it
14 would have to be modified potentially in several
15 respects, perhaps to include an extraction process.

16 A. Yes.

17 Q. Do you recall giving that
18 evidence?

19 A. Yes.

20 Q. Did you have in mind, in giving
21 that response, the kind of extraction process that
22 we have heard is utilized by Mr. Cimbura at the
23 Centre?

24 A. I think there are several
25 extraction processes for the purpose of purifying
the sample that one is dealing with.



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

1222

Ellis
re.ex. (Cronk)

1

B11

2

Q. All right.

3

A. And all of those would have
to be evaluated appropriately.

4

Q. In your view then, Dr. Ellis,
if one were to modify or develop a radioimmunoassay
technique for the purposes of conducting post mortem
tests on tissue samples, would an extraction process
be a proper and desirable ingredient in that test?

5

A. I think, in many cases, it
may be called for, yes.

6

Q. Thank you.

7

And I believe you indicated as well,
in answer to a number of questions put by various
counsel, that you were not familiar with, and had not
used, either the Beckman kit or the Beckman antibody;
is that correct?

8

A. That's correct.

9

10

11

12

13

14

15

16

17

18

19

—

20

21

22

23

24

25



DM.jc
C 1

2 Q. Would I be correct then in taking
3 from that answer, Dr. Ellis, that you are not
4 familiar with the restrictions, if any, that the
5 Beckman Company attach to their RIA kit for the
6 purposes of conducting digoxin assays?

7 A. That is correct.

8 Q. And just one final point on that,
9 Dr. Ellis, you may recall that in the cross-examination
10 conducted by Mr. Bogart yesterday he directed to you
11 questions regarding the quantity of whole blood that
12 would be necessary to result in a sufficient quantity
13 of serum, or plasma, for the purposes of conducting
14 a digoxin assay. Do you recall that discussion?

15 A. Yes.

16 Q. Can you help me Dr. Ellis,
17 during the period July 1980 to March 1981, did you
18 in your Laboratory in fact conduct digoxin assays on
whole blood?

19 A. No.

20 Q. Do you now?

21 A. No.

22 Q. In the intervening period
23 between March '81 up to today's date as we sit here,
are any digoxin assays conducted on whole blood in
the Hospital to your knowledge?

24

25



ANGUS. STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Ellis, re.ex.
(Cronk)

1224

C.2

1

A. To my knowledge, no.

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Thank you. You may recall as well in addition to that particular area, Mr. Bogart during his cross-examination drew your attention to a discussion that you and I had had in your evidence in chief with respect to the drugs that may or may not have been tested by Antibodies Inc. for cross-reactivity, or the absence of cross-reactivity with the anti-serum that that company provides. He referred you in that regard to furosemide, propanolol, if I am pronouncing it correctly?

A. Propanolol.

Q. I am not going to try it again, Dr. Ellis, and the third quinidine, do you recall that discussion?

A. Yes.

Q. First of all, can you tell me when you refer in that context to anti-serum, is that word interchangeable for the purposes in this context with the antibody that is supplied by Antibodies Inc.?

A. Yes.

Q. Now, I was left with some confusion undoubtedly through my own error, as to what your evidence was in that respect. As I



C.3

1

2 understood what you told Mr. Bogart, you said the
3 supplier could not test those drugs for cross-reactivity
4 with the anti-serum provided by Antibodies Inc., do
5 I have that correctly?

6

A. The supplier could not have
tested for those drugs?

7

Q. Yes.

8

A. No, I don't think I said that.

9

Q. That is why I want to clarify
it, Dr. Ellis, because I am uncertain in my own mind.
Technically, could those drugs have been tested for
cross-reactivity by Antibodies Inc. as the supplier
of that antibody?

10

A. Yes, they could.

11

Q. To your knowledge, was that done?

12

A. To my knowledge, I don't have
any information on that.

13

Q. Thank you.

14

A. On all the specifics that you
mentioned, but for the reasons that I explained
yesterday there would be a logical reason why they
wouldn't necessarily test all those drugs. Simply
because the interference that was alluded to several
weeks ago I think where a large number of drugs were
mentioned. I think Mr. Cimbura was asked about this.

15

16



C.4

1

2 Where there were a very large number of drugs
3 interfered with his assay, to his knowledge, and
4 basically the point I was trying to make was you
5 could divide that large group of drugs into two
6 groups.

7

Q. Yes.

8

A. One of which if you took the
drug and added it to your assay system you could get
interference. For example, if you took digitoxin
you could get interference in your assay system.

9

The other group of drugs are drugs
which if co-administered with digoxin to a patient,
the true digoxin of that patient may increase as a
result of the co-administration of that drug, and I
believe that one such drug is quinidine, for example.
So there is no structural similarity, to my knowledge,
in the chemical structure of quinidine and digoxin
and there would be no indication for assaying it in
the assay system, in the radioimmunoassay system. So
I was just trying to clarify that rather confused
area.

10

Q. Thank you, Dr. Ellis. To be
fair to you, as I understand what you have just said,
the issue as to whether or not there was any utility,
or whether it was desirable for any reason to test

11

12



C.5

1

2 on the assay those three drugs for cross-reactivity
3 is one issue?

4 A. Yes.

5 Q. The other issue is whether or
6 not technically it could be done to determine whether
7 or not they were in fact cross-reactive. Am I correct
in that?

8 A. Yes. You could technically take
9 every drug in the pharmacopeia or whatever solution
10 you cared to make, assuming it dissolved, and put it
11 in the assay system if you so wished.

12 Q. Thank you. If a physician or
13 a biochemist had any reason to inquire into the
14 cross-reactivity of any drug to the digoxin antibody,
15 technically a cross-reactivity test could be run in
respect of that drug, is that correct?

16 A. Yes, assuming this was soluble
17 under the conditions that this dissolved in the
18 solution.

19 Q. So for example in respect of
any patient, a hypothetical patient, if you knew that
20 certain drugs had been prescribed to that patient
21 it would technically be possible to run a test on
22 each and every one of those drugs for cross-reactivity
23 of the digoxin antibody that is in use in the
24 hospital?

25



C.6.

1

2 A. I think in general one could
3 say that.

(2)

4 Q. And you may recall as well, Dr.
5 Ellis, that during the cross-examination of you by
6 Mr. Strathy yesterday, your attention was drawn to
7 the recent studies and the recent published articles
8 concerning what has been called in this courtroom
9 "Substance X", do you recall that?

10

A. Yes.

11

Q. And as I understood the exchange
12 yesterday it was suggested to you that in light of
those recent studies there is difficulty in relying
13 on the radioimmunoassay technique for digoxin testing
on very young children. Do you recall that?

14

A. Yes.

15

Q. As I recall it as well Mr. Strathy
questioned you with respect to, as Mr. Scott referred
to earlier this morning, the number of patients in
the Hospital between July 1980 and March 1981 that
were experiencing toxic digoxin levels, do you recall
that?

16

A. Yes.

17

Q. And you previously told us that
in the area, if I have your evidence right, that in
the area of interpretation of results of readings from

18

19



C.7.

1

2 a digoxin assay, levels recorded by the use of the
3 radioimmunoassay technique cannot be regarded in
4 isolation from the clinical history, or the clinical
5 pattern of a particular patient, is that correct?

6

A. Yes.

7

Q. Would you agree with me, Dr. Ellis, I am trying to confirm whether or not my understanding of this particular issue is correct, that dealing with the case of very young children as referred to by Mr. Strathy, it is possible for very young children to record on a digoxin assay a level of 2 nanograms per millilitre, 2.5 nanograms per millilitre or higher, yet having regard to their clinical condition not be in the toxic range?

14

A. Yes, not be in the toxic range, or not show clinical symptoms of toxicity.

16

Q. Well, let's take it in two parts. Is it possible, based on your experience, dealing again with very young children, for a digoxin level to be recorded of 2 nanograms plus, and yet upon interpretation of those results it could be determined that the particular child was not experiencing toxicity from digoxin?

22

A. Yes.

23

MR. SCOTT: Mr. Commissioner, I don't

24

25



C.8

1

2 mean to interrupt. This is a point of some confusion
3 which I hoped I had cleared up, but perhaps I failed.
4 The expression "toxic range" perhaps Miss Cronk can
5 pursue this, is a numbers game. If you are above a
6 certain level you are in a toxic range, it has
nothing to do with whether it is in fact toxic.

7

MS. CRONK: That is my point.

8

MR. SCOTT: That is whether it is
poisoning somebody.

9

10 MS. CRONK: That is my point, Mr.
11 Commissioner, and perhaps I have expressed it badly.

12

13 THE COMMISSIONER: Is this the right
witness to ask that question of?

14

15 MS. CRONK: Well, I am not asking
Dr. Ellis for obvious reasons, what his view of an
appropriate interpretation would be. The understanding
16 that I took away from the cross-examination conducted
by Mr. Strathy yesterday in respect of this matter,
17 I just want to make it very clear if I have it
correctly, that as far as Dr. Ellis is concerned that
18 a reading alone from a very young child of 2 or
better than 2, is not necessarily indicative of
19 digoxin toxicity.

20

21

22

23

24

25

THE WITNESS: Is not always associated
with clinical signs and symptoms of digoxin toxicity.



C.9

1

2 MS. CRONK: Fair enough, fair enough,
3 thank you, Dr. Ellis.

4 Q. One final point, Dr. Ellis. You
5 will recall yesterday, and again my friend Mr. Scott
6 referred to this this morning. Mr. Hunt having a
7 discussion with you concerning the distinctions
8 between the practice and discipline of a clinical
9 biochemist and a forensic biochemist. I wanted just
10 to be again clear in my own mind as to what your
11 evidence had been in that respect because I thought
12 I had understood your evidence on Thursday and I came
away with some confusion yesterday.

13

14

15

16

-

17

18

19

20

21

-

22

23

24

25



DP, jc
D 1

2 Am I correct, Dr. Ellis, that you
3 personally have had no experience with the HPLC
4 testing method for digoxin assays?

5 A. Yes.

6 Q. Have you had any experience
7 with what has been called the HPLC mass spectrometry
8 technique for digoxin assays?

9 A. The HPLC --

10 Q. MS, mass spectrometry. I perhaps
11 am saying that wrong, for digoxin assays?

12 A. I have not, no, but I don't
13 believe Mr. Cimbura has either. I don't think there
14 is anybody in Canada who has had experience in that.

15 Q. But in any event, you, sir, have
16 not?

17 A. No.

18 Q. Am I correct as well that in the
19 RIA testing and the assays done at the Hospital you
20 have not had experience with what has been referred
21 to as the double antibody system, that is, an antibody
22 used for the purposes of attracting the patient
23 digoxin or the radioactive digoxin and the second
24 antibody used for the purposes of separating the bound
25 digoxin from the unbound digoxin. You have not had
experience with the double antibody system?



D.2

1

2 A. I have had quite a lot of
3 experience with double antibody systems for assays
4 other than digoxin.

5 Q. I am sorry, I meant for digoxin
6 assays. So it is correct that for digoxin assays
7 you have not used that kind of a system?

8 A. Yes.

9 Q. Thank you.

10 Similarly, am I correct, Dr. Ellis,
11 that you have had no experience with the creating of
12 a radioimmunoassay technique or indeed any other kind
13 of assay technique purely for the purposes of running
14 digoxin assays, because when you joined the Hospital
15 for Sick Children that technique was already in place.
16 Is that correct?

17 A. Yes. We have tried modifying it
18 in various ways but essentially we come back to the
19 same point, more or less.

20 Q. Am I correct then that you have
21 not been required to design and implement a system
22 for digoxin assays, from scratch?

23 A. No.

24 Q. Similarly, am I correct, Dr. Ellis,
25 that you have had no experience with adapting your,
and by your I mean the RIA assay system that is in use



D.3

1

2 at the Hospital, for the purposes of conducting post
3 mortem tissue sampling assays?

4 A. Yes, I think I indicated this
5 before.

6 Q. That adaptation has not taken
7 place?

8 A. Yes. I have not spent a lot of
9 time doing that, no.

10 MS. CRONK: Thank you. Thank you for
11 your patience, Dr. Ellis. I have no further questions,
12 Mr. Commissioner, unless you do?

13 THE COMMISSIONER: Thank you, Doctor.

14 MS. CRONK: Thank you very much, sir.

15 Our next witness is Dr. Steven Soldin
16 from the Hospital for Sick Children.

17 DR. STEVEN SOLDIN, Sworn

18 THE COMMISSIONER: Is that a "v" or a
19 "ph" in Steven, Doctor?

20 THE WITNESS: With a "v".

21 THE COMMISSIONER: Thank you.

22 DIRECT EXAMINATION BY MS. CRONK:

23 Q. Dr. Soldin, I have handed to you
24 a copy of your curriculum vitae which was provided to
me by your Counsel. As I understand it, you were born
in Johannesburg, South Africa, in October of 1940. Is
that correct?

25



D.4.

1

2

A. That is correct.

3

Q. And you obtained a Bachelor of
Science Honours Degree in Chemistry in 1962?

4

A. Correct.

5

Q. Can you tell me where you obtained
that degree, sir?

6

A. University of Witwatersrand.

7

Q. I am sorry, can you repeat that?

8

A. University of Witwatersrand.

9

Q. In South Africa?

10

A. In Johannesburg, yes.

11

Q. And was that also the university
where you later obtained in 1965 a Master of Science
in Organic Chemistry?

12

A. That is correct.

13

Q. Did you as well obtain your Ph.D.
in Biochemistry from that university in 1968?

14

A. Yes.

15

Q. And you obtained, as I understand
it, a Diploma in Clinical Chemistry in 1976 from the
University of Toronto?

16

A. Right.

17

Q. And you have had, as I understand
it, a varied work experience in that you have held
various positions both in a research capacity and as

18

19

20



D.5

1

2 lecturer both here and in South Africa from the
3 period 1964 through to 1972?

4 A. Right.

5 Q. And from August 1972 to
6 September of 1974, as I understand it, in looking at
7 your curriculum vitae, you were employed variously
8 at the University of Toronto as a Lecturer in
9 Clinical Chemistry, at St. Michael's Hospital and
the Hospital for Sick Children?

10 A. Right.

11 (2) Q. During that period of time, can
12 you tell me, sir, in what capacity you were employed
13 by the Hospital for Sick Children. We are talking
14 1972 to 1974?

15 A. I was involved in the Diploma
16 Program at that time which means that I was a student
17 at both hospitals mentioned, St. Michael's and Sick
18 Children's Hospital.

19 Q. Thank you, Doctor. I take it
20 at a subsequent time in June of 1975 you joined the
21 staff of the Hospital for Sick Children?

22 A. Yes.

23 Q. And you did so at that time, if
24 I have it correctly, sir, as Assistant Biochemist in
25 the Biochemistry Department?



D.6

1

2 A. Right.

3 Q. And that was in the Service
4 Division as opposed to the Research Division of the
5 Biochemistry Department?

6 A. Correct.

7 Q. And subsequently, as I understand
8 it, you became at some point an Associate Biochemist
9 in that Department?

10 A. Right.

11 Q. Can you tell me when that
12 happened?

13 A. October of 1978.

14 Q. And in April of 1980 you became
15 an Associate Professor with the Departments of
16 Clinical Biochemistry and Pharmacology at the University
17 of Toronto?

18 A. Right.

19 Q. And you continue today to hold
20 those appointments?

21 A. Yes.

22 Q. I note from your curriculum
23 vitae again, Dr. Soldin, that you became Director of
24 what is known at the Hospital as the Therapeutic
25 Drug Monitoring Program. Is that correct?

A. Correct.



D.7

1

2 Q. When did you become Director of
3 that Program?

4 A. Actually that was mid-October
5 of 1981. The Letter of Appointment I believe was
6 mid-October of '81.

7 Q. Did that coincide, Dr. Soldin,
8 with the introduction of the Program itself in the
9 Hospital? Had there been a Director of that Program
prior to yourself?

10 A. No, there had not been.

11 Q. You were the first Director?

12 A. Right.

13 Q. Are you today still the Director
of the Therapeutic Drug Monitoring Program?

14 A. I am, yes.

15 Q. Are you still an Associate
16 Biochemist at the Hospital?

17 A. I am, yes.

18 Q. In your capacity as an Associate
19 Biochemist, to whom do you report?

20 A. To Dr. Hill, as Associate
Biochemist.

21 Q. And in your capacity as Director
22 of the Therapeutic Drug Monitoring Program, to whom do
23 you report?

24

25



D.8

1

2

A. Currently?

3

Q. Currently.

4

A. To Dr. Goldberg and Dr. MacLeod.

5

Dr. Goldberg is Biochemist-in-Chief and Dr. MacLeod
is Director of the Division of Chemical Pharmacology.

6

Q. And as well you belong to a
number of professional organizations and associations,
and, to use Mr. Lamek's phrase, I do not propose to
embarrass you by going through those at length, but
they are set out in your curriculum vitae. Is that
correct?

11

A. Yes.

12

Q. As well, you have either authored
or co-authored a number of articles in the area of
Clinical Biochemistry?

15

A. Right.

16

MS. CRONK: Could I ask that the
Curriculum Vitae be marked as the next exhibit, sir?

18

THE COMMISSIONER: Exhibit 23.

19

--- EXHIBIT NO. 23: Curriculum Vitae of
Dr. Steven John Soldin.

20

21

22

23

24

25

MS. CRONK: Q. I ask you, Dr. Soldin,
whether your appointment as Director of the Therapeutic
Drug Monitoring Program coincided with the introduction
of that Program in the Hospital?

Can you tell me, prior to October of



D. 9.

1

2 1981 was there a formalized Therapeutic Drug Monitoring
3 Program in the Hospital?

4 A. There was no formalized
5 Therapeutic Drug Monitoring Program. Drug monitoring
6 did occur but it was scattered throughout the
7 Hospital.

8

9 If you go back in the history of the
10 drug monitoring at Sick Childrens I believe I am
11 correct in saying that the first drug that the
12 Chemistry Division was responsible for measuring was
13 in fact digoxin, and that occurred in 1974.

14

15 Prior to that, no drugs were assayed
16 within the Service Division of the Chemistry Department.

17

18 MR. SCOTT: Dr. Soldin, it might be
19 helpful if you could try and give Ms. Cronk a little
20 attention, but the Commissioner is entitled to a
21 little too, so if you could just face around --

22

23 THE COMMISSIONER: Could you move the
24 thing down a bit. I think Mr. Scott's suggestion may
25 be helpful. We may have to do some geographical
26 changes because it is natural to.

27

28 MS. CRONK: Would it be easier, sir, if

29

I move to the other lectern?

30

31 MR. SCOTT: The "people's lectern".

32

33 MS. CRONK: The people's lectern.

34

35



D.10

1

2 THE COMMISSIONER: It might be. Is
3 it just as convenient?

4 MS. CRONK: I have no difficulty with
5 that at all.

6 THE COMMISSIONER: It depends - if you
7 have a tremendous number of documents it is easier
8 to get close to the witness but there is a tendency,
9 and it is the polite thing to do, to speak to the
10 person who is speaking to you, but sometimes other
11 people are listening.

12 THE WITNESS: I apologize for that.

13 THE COMMISSIONER: No, no, no, it is
14 not your fault. It is our fault.

15 MS. CRONK: Thank you, Mr. Commissioner.
16 I am sorry I did not perceive that earlier.

17 Q Dr. Soldin, returning to the
18 question of when the program was formally introduced
19 to the Hospital, do I take it then - you indicated
20 that the drug monitoring did take place but it was
21 scattered at the Hospital.

22 Do I take you in that sense to mean
23 that there were physical areas within the Hospital
24 where drug monitoring was carried out?

25 A Right. Prior to 1974, no drug
monitoring occurred in Chemistry. In 1974 I believe



D.11

1

2 the digoxin assay was introduced in the Chemistry
3 Division, the Service Division of the Biochemistry
4 Department. Some monitoring occurred of anticonvulsant
5 drugs in a research laboratory that was run by
6 Dr. Lowden at this time. So that was again a
7 different laboratory.

8

I cannot tell you when the Department
of Microbiology became involved in the measurement
of aminoglycosides. I do not have that information.

9

Q. Can you help us, Dr. Soldin,
with what the purpose of the Therapeutic Drug
Monitoring Program is as it has now come to be in the
Hospital?

10

A. The overall purpose has to be
in an attempt to optimize patient care.

11

Perhaps at this point I could spend a
few minutes discussing the rationale for therapeutic
drug monitoring.

12

Q. I understand in that regard,
Dr. Soldin, that you brought with you a number of
slides which you think might graphically explain to
the Commissioner and others present what the purpose
of the Program is. If this is an opportune time,
perhaps you could show them to us.

13

14

15

A. Thank you.



D.12

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Can you tell us what that slide
is intended to depict, Dr. Soldin?

A. As Dr. Ellis has mentioned,
there are thousands of drugs in the pharmacopeia and
yet there are only a few drugs which therapeutic
drug monitoring is used for in the improvement of
patient care. You can ask yourself why is this so?
Basically the drugs have to meet certain clear
criteria before therapeutic drug monitoring becomes
a useful practice.

This slide is taken from some work
which was carried out at the Massachusetts General
Hospital several years ago and they were looking at
adult patients, 200 patients of epilepsy and all of
these patients were being treated with phenytoin and
all of them were receiving the same dose of drug,
namely 300 milligrams per day.



Soldin
dr.ex. (Cronk)

1

6 jul 83
E
BMcra

2 The samples were drawn for analysis
3 at the appropriate time for sampling, which is just
4 prior to the next dose, and the serum concentration
5 of this drug phenytoin.. was then measured in these
6 200 patients.

7 As you can see, a large -- we get
8 quite a scattered range of serum concentrations.

9 Now, the therapeutic range for this
10 particular drug is usually thought to be between
11 10 and 20 mg per litre and, in fact, only something
12 of the order of 28 per cent of the results fell within
13 10 and 20 milligrams per litre; that is, there were
14 fully some 60 per cent of the results that fell
15 below what is the accepted therapeutic range for
16 phenytoin in the treatment of seizures.

17 Q. If I can interrupt you, Dr.
18 Soldin, was the same amount of drug administered to
19 each of the 200 patients?

20 A. Right, 300 mg of phenytoin
21 was administered to each of these patients.

22 Only some 28 per cent had concentra-
23 tions within the therapeutic range and some 12 per
24 cent had concentrations in the toxic range.

25 What this study clearly identified
26 was that, if you give a certain dose of this drug



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

1245

Soldin
dr.ex. (Cronk)

1

E2 2 to patients, you cannot predict the serum concentration which will arise, and only some 28 per cent -
3 which is a rather small percentage - had concentrations within what is regarded as the acceptable
4 therapeutic range.

5

6 Q. If I could stop you there,
7 Dr. Soldin. Does the amount of concentration of
8 serum as a result of the administration of the drug
9 depend on the clinical condition of the patient?

10

A. I'm sorry, could you rephrase
11 that for me?

12

Q. Yes.

13

MR. SCOTT: While it is being re-
phrased, I don't want to be the stage director, but
14 it might be a little easier if you stood over on the
15 other side of the screen. We really must start
16 paying a little attention to the Commissioner here.

17

THE COMMISSIONER: Well, don't spoil
18 him! Perhaps you might back up here and use this
other one.

19

MS. CRONK: Thank you, Mr. Scott.

20

If you pick that up too far, Mr.
21 Scott, we're in a lot of trouble!

22

MR. SCOTT: If we could get this
23 around this table leg, we're in business.

24

25



E3

1

2 THE COMMISSIONER: While we are
3 considering all these stage directions, Doctor,
4 you said 12 per cent were in the toxic range; do I
have that correct?

5

THE WITNESS: Yes, approximately.

6

7 THE COMMISSIONER: It seems to me
8 that none of them were in the toxic range but 10
9 to 20 was therapeutic. Maybe I don't understand
that.

10

11 THE WITNESS: Well, you can see that
many of the patients had concentrations greater than
20; in fact, approximately 12 per cent.

12

13 THE COMMISSIONER: All right. I see.

14

15 THE WITNESS: Had concentrations
greater than 20, which very often is associated with
toxicity for this particular drug.

16

17 THE COMMISSIONER: The concentrations,
then, I take it, are at the bottom? Is that the
figure?

18

19 THE WITNESS: Correct. Concentrations
are at the bottom.

20

21 THE COMMISSIONER: I see. Well, on
the side, you have --

22

23 THE WITNESS: That's just percentage
of patients having particular concentrations.

24

25



1

E4 2 MS. CRONK: Q. Do I take it, then --
3 I'm sorry, Mr. Commissioner.

4 THE COMMISSIONER: No, no, I'm just --
5 my mind is working, but slowly.

6 So, some of them were up, I take it,
7 if I can read this properly, up around 60; were they?
Concentrations of 60 nanograms?

8 THE WITNESS: Well, between 50 and
9 52.

10 THE COMMISSIONER: 55?

11 THE WITNESS: Nobody was over 55.

12 THE COMMISSIONER: All right.

13 MS. CRONK: Q. Do I take it then,
14 Dr. Soldin, that one of the purposes of this slide
15 is to illustrate that, even when a fixed amount of
16 a drug is administered to a set number of patients,
17 the concentration of the drug in any individual
18 patient, that may differ from the other patients in
the study group?

19 A. That is correct. In fact, that
20 is one of the prerequisites for drug monitoring. If
21 one can predict the concentration in serum very
22 accurately with a drug dose, then there is no reason
to measure the concentration.

23 Q. All right. And is that

24

25



Soldin
dr.ex. (Cronk)

1

E5 2 concentration variability from patient to patient
3 equally true, in your experience, with the drug
4 dixogin?

5 A. That's correct.

6 Q. All right. Thank you.

7 Can you tell me, Dr. Soldin, was
8 there another slide that you wish to refer to?

9 THE COMMISSIONER: This drug, what
10 was that drug called that we have for epilepsy? What
11 was the name of the drug?

12 THE WITNESS: That drug is phenytoin.
13 The older name is diphenylhydantoin. It is a drug
14 used for the treatment of epilepsy, seizures and
15 so on.

16 Essentially, this slide shows the
17 reasons why, for some of these drugs, one cannot
18 predict the serum concentration for a specific
19 dosage prescribed. The variables are in the top
20 half of the slide. The first is patient compliance.
21 The patient may or may not take the drug as required
22 or requested by the physician.

23 Now, patient non-compliance, for
24 example, has been shown to give rise to about a
25 third of the results which fall below the therapeutic
range, if one reads the literature in this area.



Soldin
dr.ex. (Cronk)

E6

1
2 If we assume that the appropriate
3 dosage is taken, there are still variables in
4 absorption. For example, the absorption of the drug
5 may vary from one individual to the next. It may
6 vary, depending on whether the drug is taken
7 together with meals or not, depending on whether
8 the drug is taken together with other medications
9 or not. There are variables in the distribution
10 of the drug because people have different sizes and
11 shapes and there are variables in the biotransforma-
12 tion or the metabolism of the drug.

13 Many drugs are metabolized by what is
14 known as the hepatic microsomal enzyme system, and
15 that system can be enhanced, or the activity of that
16 enzyme system can be enhanced, by a number of
17 factors, including drugs such as phenobarbital or
18 diet, the eating of charbroiled meat, for example, or
19 the smoking of cigarettes.

20 So, small factors can influence the
21 rate at which the drugs are metabolized or converted
22 into byproducts.

23 Then we have possible variables in
24 the excretion of the drugs.

25 Because of all these variables, it
26 is impossible, for some drugs, to predict the serum



Soldin
dr.ex. (Cronk)

1

E7 2 concentration for a given dosage that is prescribed.

3 Now, the excretion part is quite
4 important when it comes to digoxin and especially
5 when we talk about interferences from other drugs,
6 interferences in the way dixogin is handled by the
7 body by other drugs, and it has already been mentioned
8 by several people in this courtroom that quinidine
9 is one of the drugs that alters the clearance of
10 digoxin renally. And other drugs that one can think
11 of in this regard are verapamil or amiodarone or
indomethacin, spironolactone as well.

12 So that, if any patients are placed
13 on any of these other drugs, it could interfere with
14 the handling by the body of digoxin, and it could
15 alter the concentration of dixogin in the body and,
16 clearly, at that point, it would be very important
17 to measure the concentration and follow the patient
closely so that appropriate adjustment in the dosage
18 regimen can be made when required.

19 MS. CRONK: Q. If I could stop
20 you there, Dr. Soldin, for a moment.

21 You have spoken specifically about
22 the importance of the excretion factor with respect
23 to the drug digoxin. Are all the other factors that
you have described as being part of the reason for
24

25



E8

1

variability in concentration equally applicable to digoxin as they are to other drugs? Are they as relevant to digoxin as they are to others?

4

A. Well, I think the excretion route is particularly relevant.

6

Q. Fine. Thank you.

7

Is there anything further on this slide that you wish to draw our attention to?

9

A. The next requirement for a therapeutic drug monitoring that a drug has to meet is that there should be a good correlation between the serum and the pharmacological effect.

12

The next slide perhaps shows --

13

THE COMMISSIONER: I take it these slides are going to be available again in some sort of documentary form?

16

MS. CRONK: I have discussed with Dr. Soldin reproducing copies of those various slides.

18

My understanding is that you have that available?

19

THE WITNESS: I have copies here, yes.

20

THE COMMISSIONER: Yes. All right.

21

Thank you.

22

MS. CRONK: Fine.

23

A. There should be a relationship

24

25



E9

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

between the serum concentration and the pharmacological effect. In other words, there should be a concentration at which the drug is probably sub-therapeutic, another concentration at which it is probably therapeutic and, finally, a concentration at which it is potentially or possibly toxic.

This slide deals with theophylline, which is an important drug used in the treatment of asthma, and shows that these conditions are, in fact, met for theophylline; that between 0 and 10 mg per litre, theophylline is usually sub-therapeutic; it is usually effective and therapeutic between 10 and 20 mg per litre and, at concentrations greater than 20, it becomes toxic.

Now, for digoxin, the same is true, except we are not talking about 0 to 10 for sub-therapeutic, but we're talking about 0 to .8 nanograms per millilitre; for therapeutic range, we're talking about from 0.8 to 2.0 nanograms per millilitre. Potential toxicity can occur at concentrations usually above 2.0 nanograms per millilitre.

Q. Could I stop you for a moment,
Dr. Soldin.

Are the ranges that you have just given us applicable to adults or infants?



E10

1

A., They are applicable to both,
in my opinion.

2

Q. All right.

3

A. Now, the ranges are not hard
and fast rules. What we are saying is that the
majority of patients who have concentrations below
0.8 nanograms per millitre will have ineffective con-
centrations of digoxin, but in some the clinical
effects may be adequate even though the concentration
is less than the so-called therapeutic range.

4

Q. And is the adequacy of that
dosage a determination that the physician would
make once the level was known?

5

A. That's a clinical decision.

6

Q. Thank you.

7

A. The same is true for the
higher range. At concentrations above 2, you may
not necessarily have toxicity, but you may, and
that, again, is a clinical decision.

8

Q. All right.

9

We have heard evidence as well, Dr.
Soldin - and perhaps I should ask you this: Were
you present in the courtroom throughout the evidence
of Dr. Ellis?

10

A. I was, yes.

11

12



1

ELL

2

Q. All right.

3

We have heard evidence with respect
to the reference values for digoxin that are set
out in the Residents' Handbook in Pediatrics
at the Hospital, and mention is made in respect of
those reference values found at page 365, and I
am referring to Exhibit 16, to an overlap area.

4

In the values that you have just
given to us, is there, in your judgment, an overlap
area between the probably therapeutic range and the
potentially toxic range?

5

A. Yes, there is an overlap area
and, usually, this is somewhere between 2 and 3 nano-
grams per millilitre.

6

Q. I'm sorry, Dr. Soldin, the
overlap area is somewhere between 2 and 3 nanograms
per millilitre?

7

A. Between the therapeutic and
the toxic range, usually, yes.

8

Q. In respect to the drug moni-
toring program of which you are the Director, what
are your responsibilities primarily in that position?

9

A. Well, broadly, it is to
optimize the program. So, my responsibilities involve
trying to ensure that we get the right sample at the

10

11



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin
dr.ex. (Cronk)

1255

E12

1

right time because interpretation of results is
impossible very often unless that occurs.

2

Q. Does that apply to the monitoring of all drugs prescribed and administered to patients within the Hospital?

3

A. It applies especially to the monitoring of drugs which have a very short half-life; that is, they clear quickly from the body. So, the time of sampling relative to the time of dose is essential when the drugs have a short half-life.

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25



Soldin, dr.ex.
(Cronk)

1

F/DM/ak

2

THE COMMISSIONER: A short --- ?

3

THE WITNESS: Half life.

4

Q. A half life?

5

6

A. A half life. That is the time
it takes for the concentration to drop to 50 per cent
of its original concentration.

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Dr. Soldin, since the introduction in a formal way of the program in October of 1981, are assays conducted for digoxin run under the auspices of the Therapeutic Drug Monitoring Program?

A. Yes, they are.

Q. Where is the program headquartered in the Hospital in a physical sense. Are there particular facilities in the Hospital from which you perform your duties as Director of the Therapeutic Drug Monitoring Program?

A. Right.

Q. Where are they located, sir?

A. It is on the third floor,
Room 3415.

Q. Is that the main biochemistry laboratory in the Hospital?

A. It is part of the biochemistry laboratories, yes.



1

2

Q. Is it the laboratory from which
Dr. Ellis works?

4

A. No, he is across the corridor.

5

Q. Dr. Soldin, during the period
July 1980 to March 1981, I would ask you to direct
your mind to that time frame, was the laboratory in
which you then worked involved in the testing of
digoxin levels in the Hospital, during the period
July 1980 to March 1981?

10

A. No, it wasn't.

11

Q. Were you yourself involved in
digoxin assays at that time?

13

A. Not usually, no. I was involved
on the one occasion when I was the clinical chemist
on call, and so I had some involvement in one, in
a couple of the cases.

16

Q. When you say the one case and
the cases, and more evidence will be heard particularly
about samples that were or were not taken on the
children that this Commission is particularly inter-
ested in. Do I take it that you were the biochemist
on call, first of all, would that refer to the
evening shift, or the weekends, or to both?

22

A. To both.

23

Q. And when you were on call you

24

25



F3

1

2

3

might or might not be called in to do a digoxin assay on a particular sample, is that correct?

4

5

A. To do or supervise digoxin, right.

6

7

8

9

Q. Now subsequent to March of 1981, dealing with the time frame following the Inquiry period, did your laboratory become involved under your direction in conducting digoxin assays in the Hospital?

10

A. Yes, they did.

11

Q. When did that commence, sir?

12

A. In July of 1981.

13

14

15

Q. From that point on was your laboratory responsible for all or part of the digoxin assays that were being conducted?

16

17

A. At that time it was responsible for all the digoxin assays that were being conducted at the Hospital.

18

Q. And is that the situation today?

19

A. Not at the present time, no.

20

21

22

23

24

25

Q. When - let me understand this then, during the period of July 1980 to March of 1981 your laboratory was not involved in conducting digoxin assays but you yourself might have been called in on occasion if you were on call to conduct



1

2

or supervise such an assay, is that correct?

3

A. Right.

4

Q. And then starting in July of
1981 your laboratory took responsibility for all
digoxin assays in the Hospital?

5

A. Correct.

6

Q. When did that change?

7

A. That changed in the fall, I
think October or November of 1982.

8

Q. And what happened at that time?

9

A. At that time there was a great
deal of clinical pressure on the Therapeutic Drug
Monitoring Program to offer the analysis of
methhexate which is a drug used for the treatment of
cancer. In order to accommodate this particular
assay we needed more time, or staff. Staff wasn't
available and Dr. Ellis' lab was able to undertake,
to provide the measurement of digoxin during the
week, that is Monday to Friday.

10

Q. And what happened on weekends?

11

A. On weekends my staff provided
the analysis of digoxin. Also they provided the
stat analysis, that is if an urgent request occurred
during the week that urgent request was usually
done by my staff.

12

13



1

2

Q. So if I understand it correctly,

3

Mr. Soldin, after November 1982, Dr. Ellis' laboratory again resumed the responsibility for conducting digoxin assays Monday to Friday, during the week, save for emergency or stat assay requests which would be conducted by your laboratory?

7

A. And save for weekends, yes.

8

Q. Save for weekends?

9

A. Yes.

10

Q. Is that the situation as we sit here today?

12

A. Yes.

13

Q. What methodology for the conducting of digoxin assays are you currently using in your laboratory, Dr. Soldin?

15

A. We are using both radioimmunoassay and fluorescence polarization immunoassay.

17

THE COMMISSIONER: I'm sorry, could you repeat that?

19

MS. CRONK: Q. I'm sorry, Doctor, could you repeat the second?

21

A. Fluorescence polarization immunoassay.

22

Q. We have heard some reference in this Court Room, Dr. Soldin, to a methodology

24

25



F6

1
2 for the conducting of digoxin assays known as the
3 TDX, is that the fluorescence polarization immunoassay?

4 A. That is correct.

5 Q. What do the initials TDX stand
6 for?

7 A. TD probably stands for
therapeutic drug but X I have no idea.

8 Q. Am I correct that that is
9 merely the logo on the equipment supplied by the
10 manufacturer?

11 A. It is a trade name.

12 Q. And the methodology is in fact
13 as I have referred to and you have just mentioned
14 it fluorescence polarization immunoassay?

15 A. Correct.

16 Q. For the sake of convenience
17 can I refer to that as the FPIA, if I can remember
it that way, Dr. Soldin?

18 A. Yes.

19 Q. When did the hospital begin
20 to use that method for digoxin assay testing?

21 A. The history of the fluorescence
22 polarization immunoassay, at least my history with
23 it, dates back perhaps four years when Abbott who
24 market this, approached our laboratory and myself

25



Soldin, dr.ex.
(Cronk)

1
2 four years ago to evaluate a prototype of this
3 machine. This was done only for theophylline, the
4 measurement of theophylline at the time. Then
5 approximately a year ago we acquired an instrument
6 which they were then marketing at this point to
7 evaluate and we did an evaluation on that instrument
8 over a period of one month. We then, in March of
9 1983, acquired an instrument at the Hospital for
Sick Children.

10 THE COMMISSIONER: Is this a
11 different instrument or the same instrument?

12 THE WITNESS: Essentially the
13 same one that we had evaluated. Well, it is not
14 the identical machine that we evaluated.

15 MS. CRONK: Q. The same system?

16 A. The same system.

17 Q. So I can be clear about this,
18 Dr. Soldin, was the machine or the equipment that
19 you evaluated last year for 1982 supplied to you
20 by the Abbott Company that you referred to a few
moments ago?

21 A. Correct.

22 Q. Did you evaluate it for the
purposes of digoxin assays at that time?

23 A. Yes, I did.

24

25



F8

1
2
3 Q. And when you say you obtained
4 an instrument in March of this year, was the equipment
5 that you obtained again supplied to you by the
Abbott Company?

6 A. Correct.

7 Q. And that is the FPIA technique
8 or methodology, it is the hardware to permit tests
on that equipment to be conducted?

9 A. Right.

10 Q. Was that obtained for the
11 purposes of conducting digoxin assays, or assays
12 for other drugs, or both?

13 A. Both.

14 Q. Since March of this year when
15 you acquired that instrument, have you been
conducting digoxin assays on the FPIA?

16 A. Yes, we have. We again had a
17 period of evaluation which lasted again approximately
18 one month, and then we started using the instrument.
19 At the present time it is only being used for digoxin
20 for stats requests.

21 Q. By stat do I take it you mean
22 emergency?

23 A. Yes, right. So that is the
present situation. However, we have had several

24
25



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin, dr.ex.
(Cronk)

1264

1

2

3

4

5

6

meetings at the hospital evaluating the results that we have obtained on this equipment and I think within the two to three weeks we will move all the digoxin assays to the fluorescence polarization immunoassay procedure.

7

Q. And discontinue at that time conducting those particular kinds of assays on the RIA?

8

A. Correct.

9

10

11

12

13

THE COMMISSIONER: This is a totally independent procedure, is it not; that is, the FPIA procedure is all you do when you do it, is that right?

14

THE WITNESS: That is correct.

15

16

17

18

19

20

21

MS. CRONK: Q. Now, as I understand it, Dr. Soldin, from what you have told us in July of 1981, backing up, your laboratory became involved in running the digoxin assays and on various levels of involvement have been continuing to do that to date. So I take it you have had some experience in using the RIA methodology for digoxin assays in addition to the FPIA methodology.

22

A. Right.

23

Q. Is that correct?

24

A. Right.

25



Soldin, dr.ex.
(Cronk)

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

F10
Q. When you say, Dr. Soldin, that you anticipate that within the next two to three weeks all digoxin assays in the hospital will be run on the FPIA method, is that a matter that is now actively under consideration, or has a determination been made to switch fully to FPIA system?

A. That has been actively

considered and we had several meetings. We have spoken to the staff people involved, that is the head of Cardiology, the Neonatal group, and various other medical directors, et cetera. The decision has been made to switch, yes.

Q. As I understand it, Dr. Soldin, the FPIA technique is similar in basic concept to the radioimmunoassay technique, and you can correct me if my understanding is wrong. I take it that essentially the basic principle that is involved with the FPIA is once again a competition between a particular kind of molecule that has been treated in a particular way with a patient sample, a competition between those two for a binding site on an antibody that is used in the process.

A. That is right.

Q. Is that a fair statement of the basic principles?



1

2

A. Right.

3

4

Q. And I take it with the FPIA method you do not use radioactive digoxin, or a component treated with iodine 125 for radioactive purposes, but rather you use a substance that has been labelled with fluorescein, is that correct?

5

6

A. That is correct.

7

8

Q. I would like to review very briefly with the component parts of the FPIA test, Dr. Soldin. Am I correct that standards are involved in the use of this methodology as well?

9

10

A. Yes.

11

12

Q. How many standards are required?

13

14

A. There is a zero standard and five others, so there is six altogether, five plus a zero.

15

16

THE COMMISSIONER: I am sorry, there is a which standard?

17

18

THE WITNESS: There is a zero.

19

20

THE COMMISSIONER: A zero standard?

21

22

THE WITNESS: Yes, zero, 0.5,

1, 2, 3 and 5 nanograms per millilitre.

23

24

MS. CRONK: Q. And are those standards manufactured or produced for you in the hospital or do you obtain those commercially?

25



1

2

F12

A. They are obtained from Abbott.

3

Q. From Abbott Company?

4

A. Yes.

5

Q. And indeed, perhaps with
respect to each of the components of the test that
we will be discussing, are any of the components
purchased or supplied to you from other than the
Abbott Company?

6

A. Not for the conducting of
the actual assay, they are all purchased from Abbott.
Our quality control material is not.

7

Q. Well, I will come back to the
control samples in a moment, Dr. Soldin. Dealing
still with the standards what purpose do they
serve in conducting an FPIA assay?

8

A. The same purpose that they
serve in conducting an RIA assay, which is to
obtain the calibration graph so that the patient
samples can be read off this graph.

9

Q. So I take it that you use those
standards to calibrate the machine at the outset of
the assay, is that correct?

10

A. Right.

11

Q. How often, using the FPIA
method is it necessary to calibrate the equipment

12

13



1

2

F13 before running an assay?

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. Well, at this time we are calibrating once a week and that is proving very adequate. It may be that one only has to calibrate once a month, but that study we haven't yet performed. Certainly the calibration period unlike radioimmuno-assay only has to be run at the most weekly.

Q. And I take it, because we have heard evidence from Dr. Ellis, that with the RIA method it is required that the standards be used to calibrate the machine before each and every assay, do you agree with that?

A. Right.

Q. So that with the FPIA there is a marked distinction in terms of the requirement for calibration of the machine?

A. Right.

Q. And I take it a concomitant time saving involved with that?

A. Time and funding ultimately, yes.

Q. Yes, I appreciate that as well, Dr. Soldin. You mentioned quality controls. It is my understanding that like the RIA methodology, once again, control samples are required and used to



1

2 F14 conduct an FPIA test, is that correct?

3 A. Right.

4 Q. How many control samples are
5 used?

6 A. Three.

7 Q. And what are the concentrations
8 of those control samples?

9 A. I will have to look them up.

10 MS. CRONK: You will notice, sir,
11 that Mr. Scott has arranged that I am sufficiently
12 far back from the flip chart there that I can't
13 possibly do damage with it, with a felt pen in my
hand again.

14 THE COMMISSIONER: I think he under-
15 estimates you, I'm sure you can manage it if you
16 are determined.

17 THE WITNESS: 0.6, 3.1 and 1.5
nanograms.

18 THE COMMISSIONER: I'm sorry, can
19 I have those again?

20 THE WITNESS: 0.6, 1.5 and 3.1
21 nanograms per millilitre.

22 MS. CRONK: Q. When I referred to
23 concentrations in that context, am I correct that
24 that refers to a fixed amount of digoxin that is
introduced to each of the control samples?

25 A. That is right.



6jul83
G
DPra

1

Q. And where do you obtain the control samples that you use for the FPIA assay?

4

A. From Hyland.

5

Q. I'm sorry?

6

A. From Hyland Laboratories.

7

Q. Is that the exception that you referred to a moment ago, all the other required components for the test being purchased or obtained from Abbott, with the exception of the control samples?

10

A. Right.

11

Q. You indicated to me a few moments ago that the FPIA methodology does not entail the use of radioactive digoxin but, rather, digoxen that has been labelled with fluorescein; is that correct?

16

A. Correct.

17

Q. And that is the next part of the assay that is required before we come to the antibody, and that is fluorescein labelled digoxin?

19

A. Right.

20

Q. Where do you obtain that, for the purposes of conducting an assay?

22

A. From Abbott.

23

Q. And like the RIA methodology,

24

25



1
G2

2 there is a set or fixed amount of fluorescein
3 labelled added to both the standards that you use
4 on the assay and the control sample?

5 A. Correct.

6 Q. Are the standards and the
7 control samples run through the assay at the same
time that the patient sample is?

8 A. The standards, as I have ex-
9 plained, are run only once a week.

10 Q. I'm sorry, all right.

11 What about control samples?

12 A. The control and patient's
13 are run with every batch.

14 Q. And the next component part
15 is, obviously, the patient sample itself and the
16 sample of interest in respect of which the assay is,
in fact, being run?

17 A. Right.

18 Q. Is there a particular kind of
19 sample that is used on the FPIA as compared with the
20 RIA? For example, do you run FPIA digoxin assays
on whole blood samples?

21 A. No, serum or plasma.

22 Q. Is the FPIA, in fact, designed
23 to accommodate testing on tissue samples?

24

25



1
G3

2 A. Not to my knowledge.

3 Q. Have you attempted to use it
4 for that purpose since its acquisition in the
5 Hospital?

6 A. No.

7 Q. The next component, and again
8 correct me if I am wrong in my understanding, Dr.
9 Soldin, the next component of the assay is, in fact,
the antibody.

10 Do I take it that that, as well, is
11 supplied as part of the kit that you obtain from
12 the Abbott company?

13 A. Right.

14 Q. Is the purpose of that anti-
15 body in this assay similar to the purpose of the
antibody in the RIA assay?

16 A. Yes.

17 Q. By that, would I be correct
18 in taking it that its purpose -- first of all, that
19 it has an avidity or attraction for both digoxin
and for fluorescein labelled digoxin?

20 A. Right.

21 Q. And the purpose of the assay,
22 or the basic principle involved, is that the
23 fluorescein labelled digoxin will compete with the

24

25



G4

1
2 patient sample digoxin for a binding site on the
3 antibody?

4 A. Right.

5 Q. Can you tell me, Dr. Soldin,
6 in this particular assay, is there any need after
7 the interaction of the fluorescein labelled digoxin
8 and the patient sample digoxin with the antibody
9 has taken place, after that part of the step has been
10 completed, is there any need to separate the amount
of bound digoxin from unbound digoxin?

11 A. No.

12 Q. Can you tell me why that is so?

13 A. Because, here, we are measuring
14 a change in polarization which does not require such
a separation.

15 Q. Dealing with the change in
16 polarization, so I might understand that, as I under-
17 stand, the principle of the fluorescein labelled
18 digoxin is such that a polarized light is shone,
19 by virtue of the equipment, through the component
20 or the mixture that you have, which includes both
21 the fluorescein labelled digoxin and the patient
22 sample digoxin together with the antibody; is that
correct?

23 A. Correct.

24

25



1
G5

2 Q. As I understand it, the degree
3 to which the fluorescein labelled digoxin has become
4 bound to the antibody is reflected in the kind of
5 light or the plane of light that is emitted at the
6 other end of the process; is that correct?
7

A. Yes.

8 Q. How do you know whether or not
9 the fluorescein labelled digoxin has effectively won
10 the competition and more of it has bound itself to
the antibody than the patient sample digoxin?

11 A. By measuring the light intensity
12 at the other end.
13

14 Q. What do you expect to see in
15 terms of intensity if the fluorescein labelled
16 digoxin has bound itself to the antibody in a higher
17 proportion or volume than the patient sample?
18

19 A. You will get a strong signal
20 if the fluorescein labelled digoxin has linked up
21 with the antibody.
22

23 Q. And conversely, if a weak
24 signal results in the process, do I correctly take
25 that to mean that a greater proportion of the patient
sample digoxin has bound itself to the antibody than
has the fluorescein labelled digoxin?

A. Right.



G6

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. So the basic principle then is, if I understand it correctly, the lower the light that is emitted at the end of the process on a polarized plane, the greater is the amount of the patient digoxin that has become bound?

A. Correct.

Q. And conversely, the higher amount of light that you can detect at the end of the process on a polarized plane means that a greater amount of fluorescein labelled digoxin has become bound and, correspondingly, a lower amount of patient digoxin has become bound?

A. Right.

Q. How is that light measured?

Is that a function of the equipment itself, doctor, or are we talking about something akin to a gamma counter that tells you what is there?

A. It is measured by the usual way of measuring light intensity, which is by converting the light signal into an electrical signal and employing a photomultiplier tube.

Q. Is that done electronically?

A. It is done electronically.

Q. After that has been done and you have been able to identify, by the electrical



1
G7

2 reading, the amount of polarized light that has
3 resulted from the process, how do you then make
4 the step of knowing how much patient digoxin is,
5 in fact, bound and present in the sample?

6 A. When you read the result of
7 the calibration curve.

8 Q. And are we then again involved
9 in a plotting process as described by Dr. Ellis?

10 A. Yes.

11 Q. Would I be correct then, Dr.
12 Soldin, that, at the end of an FPIA assay, you know
13 how much fluorescein labelled digoxin is contained
14 in the standards and you can plot the curve of that
15 because you know the fixed amount that was intro-
16 duced into the standards at the outset?

17 A. Correct.

18 Q. And you can then compare the
19 values that you would expect to see, given the
20 known amount of digoxin in those standards; you can
21 then compare that with the reading that you have
22 obtained electronically as to the amount of fluores-
23 cein labelled digoxin in the patient sample, the
24 end compound?

25 A. Right.

Q. Am I correct as well, Dr.



G8

1
2 Soldin, that whatever else is in the patient sample,
3 there is another similarity between the RIA and the
4 FPIA method, and that is, only substances that are
5 digoxin, digoxin byproducts or that react like
6 digoxin in respect of the antibody, will be involved
7 in the binding process that takes place in the FPIA
assay?

8 A. Correct.

9 Q. Now, can you tell us briefly,
10 Dr. Soldin, in your view, what advantages there are,
11 if any, to the FPIA system versus the RIA system?

12 A. I have written up a list of
13 advantages for the Hospital and I would be prepared
14 to make it available to this hearing if you wish.

15 Q. We would be glad to see that,
doctor.

16 A. Some of the obvious ones are
17 that fluorescence polarization immunoassay as con-
ducted on the Abbott analyzer enables a digoxin
18 measurement in a very short time interval.

19 Q. How long would it take, doctor,
20 to do an assay for digoxin on the FPIA?

21 A. Approximately twelve minutes for
22 a single result and approximately 20 minutes for
23 20 results.

24

25



Soldin
dr.ex. (Cronk)

1

G9

2

Q. I'm sorry, for 20 results?

3

A. Right.

4

Q. And that is compared to what
time period, in your view, based on your experience,
on the RIA?

6

7

A. That is compared to two to
three hours on the RIA system.

8

9

Q. Is that, on the RIA system,
for one sample or for 20 or for something in between?

10

11

12

A. The difference for one and
20 is not that great; so two hours would be the
minimum for one, and a batch of 20 may take three
hours.

13

14

15

Q. Are there any other advantages
or distinctions between the FPIA methodology and
the RIA methodology?

16

17

18

A. The FPIA methodology is
extremely simple, technically, so that, apart from
being rapid, it is extremely simple, so that less
technical time is involved.

19

20

Q. And by that do you mean
personnel time?

21

A. Personnel time.

22

23

Q. Less time for the technologists
who work in the laboratory?

24

25



1
G10

2 A. Right.

3

Q. Any other advantages?

4

A. There are other possible ad-
5 vantages. The FPIA system precipitates the proteins
6 prior to analysis of the sample and, should any
7 compound be attached to the proteins that would
8 interfere with the analysis, that would thereby
remove such a compound.

9

Q. My understanding of the use
10 of the word "precipitates" in that context, Dr.

11 Soldin, is that it separates.

12

A. Separates.

13

Q. When you say that there is a
protein precipitator, do I take it that the pro-
teins are separated from the sample that you are
14 testing?

15

A. The proteins in the sample
16 are removed prior to analysis.

17

Q. Is that right at the beginning
18 of the assay?

19

A. Correct.

20

Q. How is that accomplished?

21

A. By the addition of a precipi-
tating agent, trichloroacetic acid.

22

Q. And is there a similar step

23

24

25



G11

1

in the RIA process that you use?

3

A. No.

4

Q. Is it a recommendation of the
Abbott company or is it part of the materials that
they provide to users that that precipitating agent
be used for protein separation at the beginning of
the assay?

8

A. That is correct.

9

THE COMMISSIONER: What is the
advantage of that? What is the purpose?

10

THE WITNESS: It serves several
purposes. One of the advantages that I was alluding
to is that it is conceivable, although perhaps not
proven, that a compound may be attached to a protein
or be part of a protein that might react with the
antibody to digoxin. Therefore, if you can remove
the proteins, you can eliminate that possible source
of interference.

11

THE COMMISSIONER: I just wondered,
it is not proven, but have you compared the results
from the FPIA and the RIA?

12

THE WITNESS: We certainly did. We
would never change a technique from --

13

THE COMMISSIONER: What I meant was,
has there been a difference? Have you found --

14

15



G12

1

THE WITNESS: Well --

2

3 THE COMMISSIONER: I'm getting ahead
4 of you probably.

5

THE WITNESS: You are getting ahead.

6

Let me give you an answer on that.

7

We have compared samples from patients
8 that are below the therapeutic range and going up
9 to approximately 5 nanograms per ml; that is, the
10 routine run-of-the-mill type samples that we might
11 be getting at the Hospital, and when we do such a
12 comparison, the results are extremely comparable
13 between the two techniques. So that, for clinical
14 purposes, they seem to be very comparable.

15

16

17

18

19

20

21

22

23

24

25

However, we have also done some
measurements on samples obtained on patients that
are not on digoxin and that fall in the neonatal
period; that is, under two months of age, and the
last group that we have done comparisons on is on
autopsy samples.



BB.jc
H

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

MS. CRONK: It is my intention,
Mr. Commissioner, if I could interrupt at this stage,
to deal with some of those samples in a few minutes,
if I could ask your indulgence.

THE COMMISSIONER: Yes, all right,
I'm sorry.

MS. CRONK: No, that's quite all right,
that's quite all right.

THE COMMISSIONER: Yes, go ahead.

MS. CRONK: Q. Dr. Soldin, turning to
the element of speed that you described and the
time that's required to do an FPIA assay, and you
indicated 10 minutes for one sample. Is it 10
minutes including the protein separation process, or
is that time over and above?

A. I think I said 12 minutes.

Q. I'm sorry?

A. Yes, it includes the in-time
procedure.

Q. All right. How do you know,
Dr. Soldin, if the equipment itself is functioning
properly at the end of an assay and there's been no
malfunction of the equipment. Can you protect against
that in procedures in your laboratory?

A. That's the function of the



H.2.

1
2 quality control samples which are run with every
3 single batch of patient samples. So that provided
4 we get results for the quality control samples that
5 are acceptable, and I use that word in inverted
6 commas, then we would report the results, but if
7 the quality control samples were unacceptable, then
8 there would be something wrong with the analytical
9 procedure and the results would not be reported, we
would have to find out what was wrong.

10 Q. And indeed, as I understand it,
11 one of the primary functions of running the assay
12 on the control samples at the same time that you're
13 running it on the patient sample is to determine
14 whether or not the amount of fluorescein labelled
15 digoxin that you would expect to be in the control
16 samples, because it's been put in there and you know
17 the amount of it, is in fact reflected at the end of
18 the assay so that you know that the assay is in
19 fact recording correctly, or close to correctly, the
amount that was actually in the quality control
samples?

20 A. Yes, we're interested in the
21 amount of digoxin in the quality control samples. We
22 do add fluorescein label.

23 Q. I'm sorry.

24

25



H.3.

1

A. But we're interested in the
amount of digoxin.

2

Q. The same principle is at work
with respect to the digoxin in that a known amount
of digoxin has been added to the control samples and
you can judge at the end of the assay whether the
reading corresponds, in your judgment, as being
close enough or, indeed, precisely on the amount that
you know in fact is in the control samples?

3

A. Right.

4

Q. Is that correct?

5

A. Yes.

6

Q. And that permits you to assess
whether technically the equipment is functioning
properly?

7

A. Correct.

8

Q. Thank you. Can you tell me,
Dr. Soldin, how many hospitals or laboratories in
a clinical setting to your knowledge are currently
using the FPIA method for digoxin assays, or do you
know?

9

A. This is changing monthly. So,
the latest reports we have from the American Association
for Clinical Chemistry Therapeutic Drug Monitoring
Program, of which we are a member, are that in May of

10

11



H.4

1

2 this year, 39 laboratories had basically switched
3 from RIA, radioimmunoassay to fluorescence polariza-
4 zation immunoassay; that is somewhat over 10 per cent
5 of the total number of laboratories in this program
6 in North America. There are 385 laboratories that
7 are associated with this program in North America.

8

Q. And of those --

9

A. For digoxin, sorry; for digoxin.

10

Q. And of those in the month of
11 May, there were 39 who were using the FPIA method
12 exclusively?

13

A. Correct.

14

Q. Did that include the Hospital
15 for Sick Children?

16

A. No.

17

Q. All right. Are any of the
18 participants in the numbers that you have just given
19 us forensic laboratories?

20

A. I wouldn't be able to tell you
21 that.

22

Q. All right.

23

Mr. Commissioner, would this be an
appropriate time for a break?

24

THE COMMISSIONER: Yes, all right,
fifteen minutes.

25

--- Short recess.



H.5

1

2 --- Upon resuming:

3

THE COMMISSIONER: Yes, Miss Cronk.

4

MS. CRONK: Thank you.

5

Q. Dr. Soldin, just before the
break, you told me about the number of laboratories
who belonged to the American Association of Clinical
Chemistry that were now using the FPIA method. Is
that exclusively in lieu of the RIA method or is it
possible that some are using them in combination as
your Hospital is?

11

A. Right. It is possible that
some are using it in combination. It is not likely but
it's possible. I should mention that those are the
number of laboratories performing digoxin in the
American Association program, whereas, the number
that perform phenytoin or another drug are totally
different.

17

Q. I'm sorry. So, when you talk
about 39 laboratories reported as at the month of
May of this year, you're talking about 39 labs using
the FPIA technique for digoxin assays?

21

A. Correct.

22

Q. Do you have the number for the
month of June?

23

A. Not yet, no, but we will shortly
have.

25



H.6

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Thank you. Dr. Soldin, we also heard evidence through Dr. Ellis that at some point in time the Hospital, for the purposes of the RIA digoxin assay, ceased purchasing its standards commercially and they began to be made in the Hospital itself and his evidence was, if I recall it correctly, that you were preparing standards for the RIA assay. Is that correct?

A. My laboratory was preparing it.

Q. I'm sorry, your laboratory?

A. Yes.

Q. When did your laboratory begin to prepare those standards for use on the RIA assay?

A. I think it was - we took over the assay in July and I think we started preparing standards in August or September.

Q. Of 1981?

A. Of 1981.

Q. All right. And in the preparation of these standards, do I understand it correctly that what that involves is measuring a known amount of digoxin to be introduced and used as the standards sample both to calibrate the equipment for the RIA assay and then to be run through the assay itself?

A. Right.



H.7

1

2 Q. All right, thank you. You

3

4 mentioned again, dealing with the FPIA technique, you
5 have told us about the time saving that's involved
6 in using that technique as opposed to the RIA
7 technique, both because the assay itself requires
8 less time and perhaps as a corollary of that, because
9 it involves less technologists' time. Now, am I
10 correct, Doctor, in terms of the functioning of the
11 equipment itself, there's a time saving involved
12 first because one need not calibrate the equipment as
frequently as one is required to do so on the RIA?

13

A. Right.

14

(2)

15 Q. All right. And, secondly, you
16 have told us that there is no separation technique
17 required or precipitation technique to determine or
18 separate the amount of bound digoxin from the amount
19 of unbound digoxin and the removal of that necessity
20 would as well be a time-saving factor. Is that correct?

21

A. Correct.

22

19

20 Q. And in addition to that, I take
21 that to mean that there is no charcoal involvement,
or there is no reagent introduced to the assay to
accomplish that?

22

A. Correct.

23

24

Q. All right. And the third area

25



H.8

1

2 in which there would be a time saving, apart from
3 technologists' time itself, is that there is no use
4 of a gamma counter to do an actual reading, that
5 there is an electronic reading done automatically
6 on the FPIA for the purposes of measuring the amount
7 of polarized light that is evident or existent at
8 the end of the assay, that's done automatically by
the equipment?

9

A. Yes.

10

Q. And finally, am I correct that
11 there is also a time saving involved in the FPIA
12 technique because as the charcoal separation step is
not required, there is no requirement for the samples
13 to incubate with the addition of the charcoal. They're
14 not required to sit on the counter and incubate for
15 a period of time as Dr. Ellis described?

16

A. There is an incubation step as
part of the procedure, but it is a short incubation
which occurs within the machine.

19

Q. All right. Now, you have told
us, Dr. Soldin, what in your view are some of the
advantages of the FPIA technique. Are there in your
view any disadvantages to that technique as opposed
to the RIA methodology?

23

24

25

A. The sample requirement for the



H.9

1

2 FPIA is somewhat greater as currently used. 200
3 microlitres of serum or plasma are the recommended
4 volumes required.

5

Q. For the FPIA?

6

A. For the FPIA. We have done
7 studies showing that results can be obtained if one
8 employs 100 microlitres of sample specimen. So that
9 in the rare instances where we don't get sufficient
10 volume, we will be able to dilute the sample with
drug-free plasma and obtain a result.

11

Q. That's in circumstances where
12 you were not supplied with 200 microlitres of
sampling?

13

A. Right, 200 microlitres of serum
14 or plasma, not of blood.

15

Q. All right, well let's deal with
16 that. What quantity of whole blood would be required
17 to produce, for the purpose of the assay, 200 micro-
18 litres of sera or plasma?

19

A. Again, as Dr. Ellis mentioned,
20 that depends on the hematocrit rate in the patient for
21 children other than young neonates, the hematocrit rate
may be around 50 per cent. So, one would need to
22 double cover the volume of whole blood. So, for
23 older children half a ml. of blood would be adequate.

24

25



H.10

1

2 For young neonates, if the hematocrit rate is, say, 70
3 per cent, one would need a better sample.

4 Q. So, it would depend on the
5 patient's age?

6 A. To some extent, yes. It
7 depends on the hematocrit rate, which is usually over
8 50 per cent in neonates and in prematures. So, it
9 may run as high as 70 per cent, maybe even 80 per cent.

10 Q. And you've told us, Dr. Soldin,
11 that you have conducted studies on the FPIA which
12 indicates that it is possible, although I take it it
13 is not desirable for you to run assays on that
14 technique with 100 microlitres of plasma or serum as
15 opposed to the desired 200 microlitre sample?

16 A. Correct.

17 Q. All right. It is possible to
18 do an assay on less than 100 microlitres of sample?

19 A. It is, but it depends on the
20 concentration of digoxin in that sample. Now, I'm
21 talking about measuring it for concentrations between
22 0.8 and usually 2.0 nanograms per millilitre. I
23 wouldn't be happy with using a very much smaller
24 sampler at the low concentration range, but if the
25 concentration in the sample is higher, then surely
one can add quite a smaller value.



H.11

1

2 Q. And do I take it that like with
3 the RIA, the situation is similar with the FPIA and,
4 that is, the smaller quantity the sample provided
5 for testing, the lower the likelihood that increasing
6 number of dilutions can be made, the size of the
7 sample directly relates to the number of dilutions
8 that one can technically perform?

9

A. Correct.

10

Q. And dealing again with the FPIA,
11 other than the size of the samples required for
12 testing, are there any disadvantages in your view to
13 this technique as opposed to the RIA methodology?

14

A. If one works out the cost per
15 analysis and projects that over a year, the cost per
16 analysis for a digoxin assay is marginally higher than
17 with the FPIA method. So that it would result in an
18 increase in our budget for the Therapeutic Drug
19 Monitoring Program of approximately \$1,000 per year.
That's about the only other drawback.

20

Q. Other than economic factors or
21 increased costs caused by this method as opposed to
22 the RIA, is there anything intrinsic to the methodology
23 itself which, from your view as a scientist, could
be considered as a disadvantage with this methodology
as opposed to the RIA?

24

25



H.12

1

2 A. Not to my knowledge, no.

3

Q. I'm correct, Doctor, am I not,
4 from the evidence that you have given, that a
5 different antibody is used on the FPIA system than
6 is used on the RIA in that the antibodies used on the
7 RIA at the Hospital are obtained from Antibodies Inc.
8 from California, whereas, the antibodies that are
9 used in the FPIA technique are obtained as part of
the Abbott Kit?

10

11

12

A. Correct, but then again I don't
know where Abbott gets their antibody. So, it may
be that they get their antibody from Antibodies Inc.

13

Q. Oh, I see.

14

A. It may not be.

15

Q. Have you made inquiries in that
regard?

16

17

A. I don't know. No, I haven't
made any.

18

19

20

21

22

23

24

25

Q. All right. Dealing with the
FPIA technique, we've heard evidence as well as to
what has been described as the minimum detection
level on the RIA, and by that, at least my under-
standing of the concept, is, as a level -- excuse me,
as a measure, the lowest measurable level or
concentration which can be distinguished from zero in



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin, dr.ex.
(Cronk)

1294

H.13

1

2 any degree of scientific confidence, is there a
3 minimum detection level that applies to the FPIA
4 technique?

5 A. There is, the same as there is
6 for the RIA technique. The problem is in deciding
7 what that detection level is.

8 Q. Well, as you sit here today,
9 as you have used that technique in your laboratory,
10 what is the minimum detection level that you treat
11 as the guideline?

12 A. Well, at the present time, we
13 employ the same lower cutoff limit as we do for the
14 RIA, which is 0.5 nanograms per millilitre. The
15 Abbott literature, that is the literature from Abbott
16 would indicate .2 nanograms per millilitre could be
17 used as the lower cutoff. At the moment, we are
18 employing 0.5.

19 Q. Is that being done for any
20 reason other than consistency, is that a factor at all?
21
22 -
23
24
25



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

I/DM/ak

A. Well, again we are getting now into the results which we have obtained on patients that are not on digoxin and then on neonates.

Q. Perhaps I will reserve that question and ask you again when we come to discuss those test results.

Aside from the - well, you told us what the standard amount of concentrations of digoxin are in the standards that are supplied from the Abbott Company for this assay. If I understood your evidence correctly the largest concentration was .5.

A. Was 5.0.

Q. I'm sorry, 5.0?

A. 5.0.

Q. All right. So the minimum detection level is not tied in then with the amount of concentrated digoxin present in the standards?

A. One could tie it in with the lowest standard employed.

Q. Right.

A. And that is sometimes practised. So that the lowest standard employed is .5 and therefore we make a decision we are not going to report anything less than .5.



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

I.2 Q. And similarly, Dr. Soldin, we have heard evidence as to what has been described as the maximum measurement capacity on the RIA method, the highest level of digoxin that can be measured on one assay without the requirement of further dilution. Is there a maximum for highest level that is applicable to the FPIA assay?

A. Again it is the highest standard concentration which is 5.

Q. And if at the conclusion of an FPIA assay in respect of any particular patient sample a reading of 5 nanograms was obtained, what would you then do in your laboratory with respect to that sample?

A. If a reading greater than 5 was obtained we would dilute the sample.

Q. And there are ---

A. If there was sufficient sample left.

Q. Assuming that there was a sufficient amount of sample initially provided, or otherwise available to you by subsequent request, are there guidelines that you employ in your laboratory as to what the first level of dilution will be, or do you do several at the same time



1

2

I.3 depending on the amount and quantity?

3

4

5

A. One would do it two times, five times, ten times provided there is enough sample.

6

7

8

9

Q. And is there any magic to the 5 nanograms per millilitre figure if you got a result on an FPIA reading of 4.6, 4.7, 4.8, would you in those circumstances dilute or must it be 5 or greater?

10

11

A. No, it should be greater than 5, yes.

12

13

14

15

16

17

Q. Are you able to tell us, Dr. Soldin, as a result of your experience both with the RIA technique for digoxin assays and your experience with FPIA technique for digoxin assays, which methodology in your view is more reliable for the purposes of obtaining a digoxin reading?

18

19

20

21

22

23

24

25

A. Well, that is a difficult question, and the answer is somewhat subjective. I think both techniques will provide good results, adequate results for clinical purposes in the majority of cases. We have heard Dr. Seccombe and a few others talk about instances where substance X might give an erroneous result, those are relatively rare instances.



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

I.4
If one looks at total work volume of digoxin, let us say we do 20 digoxin analysis on patient samples every day, not more than one or two of those 20 would be from the Neonatal Ward and only a small percentage of those might have substance X in them. So that overall I think both methods could provide reliable clinical data.

Q. Well, Dr. Soldin, can you help me with this? You have told us that as long ago as four years ago your laboratory was approached by the Abbott Company for the purposes of creating a prototype of this methodology for use with a different drug, different kind of assay, not digoxin? I am sorry, you are hesitating.

A. That is not quite right. I was approached by the Abbott Company to evaluate a prototype that already existed.

Q. Fine. All right. Do you know when the Abbott Company first introduced on the market the FPIA system for the purposes of digoxin assays?

A. I can't give you the month, you know, I think it must be 18 months ago approximately.

Q. Would I be correct then,



I.5

1
2 Dr. Soldin, given the relatively recent introduction
3 of this technique by the Abbott Company, compared
4 at least to the RIA which you have told us was in
5 use in the hospital from 1974 onwards, that there
6 is comparatively speaking a lower volume of literature
7 available reporting upon results obtained pursuant to
8 the FPIA technique than there might be reporting on
9 results obtained from the RIA technique?

10 A. That is correct.

11 Q. And that the growth of that
12 kind of literature I assume will be of assistance
13 to you in assessing as a matter of your own
14 professional judgment whether or not the FPIA
15 technique was or was not more reliable for digoxin
assays than the RIA technique?

16 A. That is correct. We have some
17 of our own findings as well which may give us some
opinions on this matter.

18 Q. All right, and I will come to
19 that in a moment. Perhaps it is a difficulty with
20 the words reliable. Can you tell me, Dr. Soldin,
21 based on your comparative experience with both the
22 methodologies whether the one as opposed to the other
23 results in more certain, or more specific digoxin
assay recordings?

24
25



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. Well, you know I think both give equivalent results. However, if you gave me a sample and said that I could only use one method for measuring that sample, for measuring the digoxin in that sample, I would choose, with my knowledge today, to measure that sample with the fluorescence polarization technique.

Q. Is that a function of anything other than the time involved?

A. I think it does, yes, apart from the time.

Q. Can you tell me what that is?

THE COMMISSIONER: I am sorry, you are asking for the time?

MS. CRONK: No, I am sorry.

THE WITNESS: It is a function other than the time.

MS. CRONK: Q. What is there in your judgment which would encourage you to use the FPIA technique other than the factor of time on any given sample?

THE COMMISSIONER: Other than the other advantages that he has told us about.

MS. CRONK: Q. To be fair, that's right, other than the other advantages.



1

2

A. Well, we keep coming back to
the preliminary data which we have on samples of
patients that are not on digoxin. The only data
that we have in the autopsy comparisons are both
RIA and FPIA. Do you want me to go into that? If
you do then those are the reasons why I would
choose the FPIA technique.

3

4

Q. All right. Well ---

5

6

7

THE COMMISSIONER: It is more
accurate, is it? The post mortem sample, is that
what you are saying?

8

9

THE WITNESS: It could be, yes.

10

11

THE COMMISSIONER: That's not quite
the same, is it?

12

13

THE WITNESS: Well, I am, that is
as far as I will go at this point in time. If we
get into the serious of results.

14

15

16

17

18

19

20

21

22

23

24

25

MS. CRONK: Q. All right. Then

again, perhaps unfairly to you I put the question
prematurely and I will come to the question of
sampling in a moment. With respect to the antibody
that is used on the FPIA technique as supplied by
the Abbott Company, have you in your laboratory used
the antibodies provided by the Abbott Company on the
RIA technique?



I.8

1

2

A. No, we haven't.

3

Q. Is there any reason why
technically that could not be done?

4

A. It could be done.

5

Q. And if that experiment were
undertaken would I be correct that would give you
some basis upon which to measure whether there was
any difference in specificity between the antibodies
currently used on the RIA and the antibodies used
on the FPIA? Is that one might obtain?

6

A. If one compared the RIA results
with the Antibody Inc. antibody and compared the
results again by RIA but at this time use the Abbott
antibody one could get an idea of the relative
specificity.

7

Q. Yes, thank you. Dr. Soldin,
we have heard evidence as well concerning a methodology
known as the HPLC methodology that has been used for
digoxin assays. Do you personally have any experience
with using that methodology for digoxin assays?

8

A. Not for digoxin, no.

9

Q. Similarly, Dr. Soldin, have you
personally had any experience in using the Beckman
Antibody either for purposes of conducting RIA
digoxin assays, or FPIA digoxin assays?

10

11



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

I.9 A. Depending what you call

personally. I haven't done tests using the Beckman RIA kit myself. However, we approached Mr. Cimbura, I can't give you the date offhand, approximately two months ago and a post doctoral fellow who was working with us has had a very brief and preliminary look at the Beckman kit as used by Mr. Cimbura. He got the instructions from the Forensic Science laboratories, but he has carried out these tests at our Hospital.

Q. Was that testing conducted in accordance with what he understood to be the methodology employed by Mr. Cimbura?

A. That is correct, what he understood, right.

Q. My question perhaps was a little different, Dr. Soldin. To be fair to you, I take it not you personally, but have any others under your supervision attempted to use the Beckman Antibody on the RIA methodology in use in the Hospital, not Mr. Cimbura's methodology, but the approach used for RIA in the Hospital?

A. No, we haven't.

Q. And similarly as the Beckman Antibody or parts, components of the Beckman kit



1

2

I.10 been used on an experimental or research basis in
3 the Hospital on the FPIA technique?

4

A. No.

5

Q. Can you help us, Dr. Soldin,
6 as to what substances or drugs have been indicated
7 by the Abbott Company to have known levels of
8 cross-reactivity with the Abbott supplied antibody
9 used in the FPIA methodology?

10

11

A. Yes. The company does have a
hand out on this which you might want to include
in the exhibits.

12

13

14

15

16

Q. If I can just see what you're
looking at, Doctor. Doctor, are you looking at
a document which you previously provided to me
through your counsel entitled "Cardiac Glycoside
Drug Assays - TDX Digoxin"?

17

A. Right.

18

19

MS. CRONK: Copies of this,
Mr. Commissioner, have been supplied to other
counsel.

20

21

22

23

Q. Dr. Soldin, can you help me,
is this document a document provided to you by the
Abbott Company in respect of the FPIA materials
supplied to you by that company?

24

25

A. Yes.



1

2

3

4

5

Q. And does it indicate or contain any results, or information, with respect to cross-reactivity of other substances, or known drugs with antiserum in use on the FPIA Abbott kit?

6

A. Yes, it does.

7

Q. What page is that, sir?

8

A. 17.4 I think it is, Table I on 17.4.

9

Q. And dealing with Table 1, Dr. Soldin, the column on the left entitled "Compound Added", do I correctly take it that drugs of the compounds listed in that column are all of those in respect of which, to your knowledge, the Abbott Company has tested for cross-reactivity with its antiserum?

15

16

A. To the best of my knowledge, yes.

17

18

19

20

21

Q. And the next column entitled "Quantity Added", and I take that to mean as is suggested by the title the amount or volume of the compound that was added to the test sample for the purposes of running the cross-reactivity assay?

22

A. Right.

23

24

25

Q. And the third column "Average Cross-Reactivity", I take that to be the result



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

1306

Soldin, dr.ex.
(Cronk)

1

2

obtained by the Abbott Company in conducting these
cross-reactivity assays?

4

A. Right.

5

Q. Can you help me, Dr. Soldin,
besides digoxin, the average cross-reactivity is
shown as 100 per cent, I take that to be a
reflection of what the Abbott Company believes to be
the degree of specificity of the antibody to digoxin?

9

10

A. Right, it is. Is it an anti-
body raised to digoxin.

11

12

13

14

Q. Can you - and dealing with the
compounds listed immediately below digoxin, given
the similarity in their names to that of digoxin,
do I correctly take those to all be metabolites or
by-products of digoxin itself?

15

16

17

18

19

20

21

22

23

24

25

A. Right.



J/DP/ak

1

2

Q. Can you help me as to what the
205 per cent average cross-reactivity means in
respect of the compound digoxigenin?

3

4

A. That means that if one had a
concentration of one nanogram per millilitre of
digoxigenin it would read 2.05 milligrams in
nanograms per millilitre of digoxin in the assay of
the average kit.

5

6

7

Q. Do I correctly take it as well
that from these results it would appear that
digoxigenin has a larger likelihood of binding to
the antibody used on the Abbott kit than does
digoxin itself?

8

9

A. Right.

10

11

12

13

Q. And similarly with the next
compound, that would be correct, recorded at 150
per cent?

14

15

A. Correct.

16

17

Q. And with the max at 115 per

cent?

18

19

A. Correct.

20

21

Q. Going down the list of

compounds added, Dr. Soldin, I note in the fourth
grouping of compounds that a test for cross-reactivity
was run for furosemide?

22

23

24

25



1

A. Right.

2

3

Q. And that the average cross-reactivity, according to the Abbott Company was .01 per cent?

4

A. Correct.

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. As well, dealing with the next

group of compounds, progesterone, and I hesitate again to pronounce this, but the next two compounds all reflect low average cross-reactivity percentages insofar as the Abbott Company's research is concerned?

A. Right.

THE COMMISSIONER: What is the

importance or significance of the "quantity added"?

MS. CRONS: Q. Can you help us

with that, Dr. Soldin?

A. It indicates the amount that was added in order to get the reading, the particular digoxin reading, so they added 10 micrograms per millilitre of spironolactone, say, and had a cross-reactivity of 0.025 per cent.

THE COMMISSIONER: Does it affect the cross-reactivity, the fact that you have added more or less?

THE WITNESS: It would change the reading, yes. If you added 100 times as much, you



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

would get a bigger reading.

THE COMMISSIONER: All right, just for this simple mind, though, you have added 5 nanograms in this ---

THE WITNESS: Dihydrodigoxigenin.

THE COMMISSIONER: Whatever it is, and you have got a figure of 12 per cent.

THE WITNESS: Yes.

THE COMMISSIONER: If you had added one nanogram, would you have got a different figure?

THE WITNESS: That is my interpretation of the data, yes.

THE COMMISSIONER: That means that actually the cross-reactivity then is only one-fifth of 12 per cent. Is that correct?

THE WITNESS: That is my interpretation of this data.

THE COMMISSIONER: Is your interpretation the correct one, do you think?

THE WITNESS: You would have to ask Abbott that.

MS. CRONK: Q. Have you done that, sir? Have you raised any enquiries with the Abbott Company as to the meaning of the figures that



1

2

J4 appear on this table?

3

A. No, I have not.

4

5

THE COMMISSIONER: What is the
relationship between an "ug", whatever an "ug" is?

6

7

THE WITNESS: A microgram and a
nanogram. A nanogram is 10^{-9} of a gram and a microgram is 10^{-6} of a
gram.

8

9

THE COMMISSIONER: And the "ug"
stands for what, please?

10

THE WITNESS: A microgram.

11

THE COMMISSIONER: Funny initials -

12

ug equals microgram.

13

14

MS. CRONK: Q. So that for example
with respect - I'm sorry, Mr. Commissioner.

15

16

THE COMMISSIONER: A microgram is
what expression of a gram?

17

18

THE WITNESS: 10^{-6} ,
one-millionth of a gram.

19

20

THE COMMISSIONER: And the nanogram
is a billionth I suppose?

21

22

THE WITNESS: 10^{-9} .

23

24

THE COMMISSIONER: So 10 micrograms
is still vastly less than a nanogram?

25

THE WITNESS: 100 micrograms is



1

2

vastly more than a nanogram.

3

4

THE COMMISSIONER: A microgram, yes,
that is what I mean. In fact it is what, 100 times?

5

6

THE WITNESS: No, one microgram is
a thousand times more than a nanogram.

7

8

THE COMMISSIONER: Yes, but 10.

THE WITNESS: 10 would be 10,000 times
more than a nanogram.

9

10

11

12

THE COMMISSIONER: But your
interpretation is that the more that you have to
add in order to get this cross-reactivity means of
course the less cross-reactivity there actually is?

13

14

15

16

THE WITNESS: Yes.

THE COMMISSIONER: Do you have any
doubt about your interpretation? You say it is your
interpretation. Do you have any serious doubt about
it?

17

18

19

20

21

THE WITNESS: It is possible that
Abbott have converted all readings to nanograms per
ml, one nanogram per ml and have evaluated it in
that light. I think they would have misrepresented
the data somewhat if that is the case.

22

23

24

25

MS. CRONK: Q. Without otherwise
indicating on the face of the document that that
had been done, and that indication is not contained



1

2

in the document, I take it?

3

4

A. I have not seen it in the
document.

5

6

7

THE COMMISSIONER: The reason
that you might suspect that they have converted is
that the cross-reactivity is so low in some of them
that it would be hard to get much lower.

8

9

10

THE WITNESS: That indicates a
specific antibody, which is what they are trying to
show they have.

11

12

13

14

15

MS. CRONK: Q. Dr. Soldin, quite
apart from the compounds indicated on this list, do
you have any knowledge as to whether the Abbott
Company undertook and conducted a cross-reactivity
test in respect of either quinidine or propanolol?

16

17

18

19

20

21

22

23

24

25

A. No, I do not.

Q. Have you, sir, in your
laboratory since either using the FPIA method on
an experimental evaluative basis, or since using it
on a full time basis, since March of this year,
conducted any cross-reactivity tests of your own to
either compare the results with what is disclosed
on this table or to include compounds not listed on
this table?

A. We have done one or two



1

2

cross-reactivity studies on the RIA technique but not
at this point in time on the FPIA technique.

3

4

If we turn to the top of the
next page of this document, Dr. Soldin, a category
entitled "Sensitivity" I note that the document
states:

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

"The lowest measureable level is
defined as that concentration which
can be distinguished from zero with
95 per cent confidence; it was deter-
mined to be 0.2 ng/mL."

Do I correctly take it that that is
the reference provided by the Abbott Company to what
they consider to be the minimum detection level of
the FPIA system, using this antibody?

A. Correct.

Q. But you have told us that for
your purposes in your laboratory you are using the
same minimum detection level that has been used
for the RIA system, that is .5?

A. Correct.

MS. CRONK: Sir, could we mark
this document as the next exhibit, please?

THE COMMISSIONER: Exhibit 24.

---EXHIBIT NO. 24: Document entitled "Cardiac
Glycoside Drug Assays - TDX
Digoxin".



J8

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

MS. CRONK: Q. Dr. Soldin, we have heard evidence from Dr. Ellis and in passing from yourself this morning that in January of 1982 there was occasion in the hospital to run digoxin assays on patient samples in respect of patients who had not been prescribed digoxin.

Were you involved in the conducting of those tests?

A. My laboratory was involved, yes.

Q. Did you supervise those tests?

A. Correct.

Q. Can you tell me, Dr. Soldin, first, how did it come about that those digoxin assay tests were undertaken? We are talking now January of 1982.

A. There were some five infants that became ill at the same time on Ward 7F and there was no explanation for them becoming ill. Because of the sensitivity of the Hospital to digoxin and its past history, we thought it appropriate to measure the digoxin concentrations in these children and subsequently, actually, on the whole ward.

Q. Stopping there for a moment,



1

2

what is Ward 7F in the Hospital?

3

A. It is a Neonatal Ward.

4

5

Q. Is that what it was in January
of 1982?

6

A. Right.

7

8

9

10

11

these children became ill at the same time and there
was no ready indication as to why they had become
ill, did they become ill in the same way? Were
they exhibiting the same symptoms? Was there some
commonality in what they were exhibiting?

12

13

A. Apparently - right. There
seemed to be some similarity in the symptoms.

14

15

16

Q. Do I take it that none of
those five children had been prescribed digoxin in
the hospital?

17

18

A. I think that is correct. One
of the children actually ---

19

20

Q. Dealing just with the five
first that became ill ---

21

22

A. My problem is, I'm not sure
whether Hamblin was one of those five. There was
one patient ---

23

24

Q. I'm sorry, Hamblin?

25

A. Hamblin, H-a-m-b-l-i-n. There



1

2

was one patient by that name who was receiving
digoxin and whose concentrations were measured and
were therapeutic but the rest of the patients on
that ward were not receiving digoxin.

3

4

5

6

7

8

Q. Perhaps to be clear about this,
Dr. Soldin, how many patients in total from that
ward, how many were involved in the tests?

9

A. There were some 15 of them.

10

Q. Was that the total ward

11

population at that time?

A. Yes.

12

13

14

15

Q. Were the five that you described
as having become ill and exhibiting the same
clinical symptoms part of that group of 15 or are
they in addition to the group of 15?

16

A. They are part of the group.

17

18

19

Q. Of the 15, as I understand
what you have just said, one of the 15, the child
you have just described, was on prescribed levels
of digoxin?

20

A. Correct.

21

22

23

Q. And he may or may not have
been one of the five that exhibited the same
clinical symptoms of illness?

24

25

A. Correct.



1

2

Q. Did any of the other 10 appear
to be overtaken by the same symptoms that were
exhibited by the first five that you have described?

5

A. No.

6

Q. How old were these patients, in
approximate terms? They were on the Neonatal Ward.

7

A. I don't have their record here
but they were young infants.

9

Q. We have had a number of
varying definitions of neonate put forward,
Dr. Soldin, and I appreciate that that definition
is perhaps in the eye of the professional who is
asked to make the judgment. In your view, can you
approximate for us, were any of these children over
six months of age?

15

16

A. I think they were all younger
than six months.

17

18

19

20

21

Q. Can you help me, again I wish
to be fair to you, can you help me as to whether
or not they were older than - are we talking the
first month or two of life or are we talking something
older than that?

22

23

24

25

A. Most of them would have been
under two months. Were they all under two months
is something I cannot be sure about unless we look



1

2

at the records.

3

4

5

6

7

8

9

Q. The assays that were conducted,

you have described and told me were digoxin assays,
and that they were undertaken because of what I
think you described as the sensitivity to the
prior experience in the Hospital. Were the assays
that were undertaken done on ante mortem or post
mortem samples?

10

A. They were done on ante mortem

samples.

11

THE COMMISSIONER: None of them

12

died, did they?

13

MS. CRONK: Q. Did any of them die, Dr. Soldin?

14

A. One of them died.

15

Q. In respect of the one that did
die, were they ante mortem or post mortem samples?

16

A. They were post mortem.

17

Q. So with the exception of that
child, the others were all ante mortem samples?

18

A. Correct.

20

Q. What type of samples were

21

tested?

22

A. Serum or plasma.

23

Q. No whole blood?

24

A. No.

25



1

2

Q. And no cord blood samples
involved?

4

A. No.

5

6

Q. And clearly no tissue samples
involved?

7

A. No.

8

Q. Did any of these children,
the 15 children, to your knowledge at the time these
tests were conducted, have diagnosed cardiac problems?

10

11

12

A. One of them was on digoxin,
so I take it that one of them would have had some
problem.

13

Q. All right.

14

15

A. The rest, I'm not aware of
a problem but again I would ask you to ask the
clinician on that ward, looking at the case histories.

16

17

18

19

20

21

Q. Am I correct that at the time
that these tests were conducted the requisition
form that has been admitted as an exhibit before
the Commission for digoxin assays pursuant to the
Therapeutic Drug Monitoring Program would have been
in place? This is January of 1982; or do you know?

22

23

24

25



K-1 1

BBeg 2

A. The requisition I think was
in place in January of '82. I'm not 100 per cent
sure of that. It was certainly in place in
February of '82. I would have to check up whether
it was in place in fact of January of '82.

Q. All right. Well, what I'm
getting at, Dr. Soldin, is simply this. I'm
referring to Exhibit 15A, that's the first
requisition form that was introduced with, we have
heard, the Therapeutic Drug Monitoring Program and
on the face of that requisition there's a space
for various information to be inserted by the
physician who is requesting a particular assay to
be conducted and amongst the various categories
of information is the category of, first of all,
the particular drug in respect of which the assay
is being requested must be indicated on the form
and, as well, there is a space for an indication
as to the time of the administration of the last
dose. Do you have that before you, sir?

A. No, I don't. But I know the
requisition, right, you're correct.

Q. Well, sitting here today and
so far as you are aware, leaving aside the one
child who was receiving prescribed levels of digoxin,

24

25



Soldin, dr.ex.
(Cronk)

1
K-2

were any of the other 14 known by you or by those
you supervised in your laboratory to be patients
suffering from cardiac ailments, cardiac patients?

A. I didn't have that knowledge,
no. But none of the other patients were known to
be on digoxin.

Q. All right. And similarly,
at the time that these tests were conducted, to
your knowledge, did any of these patients, any of
the 15 suffer from kidney impairment or any renal
dysfunction?

A. Again, not to my knowledge.

Q. How many assays were run for
digoxin in respect of each child, Doctor?

A. Well, on the five children
two runs were performed, two assays, in other words,
on different samples drawn at different times.

Q. All right. Dealing just
with that then for the moment. I take it because
the FPIA system was not in place in the hospital
at that time, unless it was the month of January,
1982 coincidentally when it was there for
evaluation procedures, that these assays were
conducted by the RIA methodology?

A. Right.



K-3

1
2 Q. And when you say that two
3 different samples were involved, on the first assay
4 that was done, do you recall whether they were
5 plasma or serum samples?

6 A. They were serum or plasma, I
7 can't tell you which.

8 Q. All right. And on the second,
9 the same thing?

10 A. The same thing, right.

11 Q. All right. Do you know the
12 difference in time today or do you recall the
13 difference in time between when the second assay
14 was run?

15 A. They were approximately six
16 hours later.

17 Q. All right. What about the
18 other ten children, how many assays were done in
19 respect of them?

20 A. One. Well, each assay, as
21 you know, is done in duplicate.

22 Q. One duplicate assay?

23 A. One duplicate assay.

24 Q. And in respect of the other
25 five, two duplicate assays?

A. Two duplicate assays.



K-4

1 Q. In respect of each?

2 THE COMMISSIONER: The five sick
3 ones.

4 THE WITNESS: The five sick ones,
5 right.

6 THE COMMISSIONER: I imagine though
7 all the children were sick or they wouldn't have
8 been in the hospital, but these were particularly
9 sick, these five?

10 THE WITNESS: Yes.

11 MS. CRONK: Q. Can you tell us,
12 Dr. Soldin, dealing now just with the five
13 children that you have described, the first
14 category on the first digoxin assay, what were
15 the recorded levels for digoxin, if any?

16 A. I'm sorry, I will have to
17 find that.

18 Q. Well, if you could take a
19 minute, Dr. Soldin, I'm going to ask you what
20 the recorded levels were on the first assay for
21 the five children, what they were on the second
22 assay and what they were on the assay for the
23 other ten children.

24 THE COMMISSIONER: I take it the
25 levels would be different. Have we a schedule of

26
27
28
29
30



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin, dr.ex.
(Cronk)

1324

K-5 2 any kind?

3 MS. CRONK: I do not, sir.

4 THE COMMISSIONER: Yes, all right.

5 THE WITNESS: Well, let me read
6 you the results on the first assay. Baby boy Gee.

7 THE COMMISSIONER: I'm sorry, you
will have to do this slowly.

8 THE WITNESS: G-E-E, okay.

9 MS. CRONK: Well, if I could
10 make a suggestion, Mr. Commissioner. I'm not sure
11 that anything turns on the identity of these
12 children.

13 THE COMMISSIONER: No, no, no.

14 MS. CRONK: Q. Could I ask that
15 you simply read the readings off from the first
16 assay on these five children without indicating
their names?

17 A. Well, 0.4, 0.4, 1.3.

18 THE COMMISSIONER: Perhaps you
19 could give us - are they ---

20 THE WITNESS: 2.1. I'm just trying
21 to get the sequence. 0.6.

22 MS. CRONK: Q. All right.

23 A. I'm sorry, there was a sixth
one, Gee, 0.8.

24

25



K-6

1

Q. Well, can you help me --

3

A. So, we did six in duplicate.

4

Q. All right. So that one of

5

the children that was done in duplicate was not of
the group of five who shared the same clinical
symptoms, or are we talking about six children who
became ill and shared the same clinical symptoms of
illness?

9

A. You know, I'm not sure if
there were five or six that became ill. There was
one of these was a set of twins.

10

Q. Oh, all right.

11

A. Okay.

12

Q. Is it possible that the set
of twins was counted as one when you told me about
the five who became ill?

13

A. I'm not sure if five or six
came down with the same clinical symptoms.

14

THE COMMISSIONER: That's one assay
on six babies, is that right?

15

THE WITNESS: Sir, I have given you---

16

THE COMMISSIONER: The second assay?

17

THE WITNESS: One assay on six
babies, right.

18

THE COMMISSIONER: Now, could you

19

20



Soldin, dr.ex.
(Cronk)

K-7

1

give us the second assay on these?

3

THE WITNESS: So, the second one
4 was 0.4 for the first one that I have quoted.

5

MS. CRONK: Q. i.e., the same

6

level that had been referred on the first assay?

7

A. The same, right.

8

Q. And the second?

9

A. 0.4.

10

Q. The same as had been
recorded on the first assay?

11

A. Right. 1.3.

12

Q. Again, the same?

13

A. Right. 1.4.

14

Q. Now, is that a drop in respect
of the patient who had previously recorded 2.1?

15

16

A. Right. This was the patient
known to be on digoxin.

17

Q. All right. And the next?

18

A. 0.4.

19

Q. Is that a drop from the 0.6
reading on the previous assay?

20

A. Correct.

21

Q. And then the last one?

22

A. 0.4.

23

Q. And again, that's a drop from

24

25



K-8 2 the reading of 0.8 on the first assay?

A. Correct.

Q. Right. Dr. Soldin, if we leave aside for the moment the patient who was known to have been prescribed digoxin, that child had initial readings of 2.1 and 1.4 on the second assay. The highest reading of the group of the remaining five that you obtained I take it was the 1.3, and that was consistent on both assays?

A. That's right, yes.

Q. All right. And of the other four, two readings consistently on both assays were less than .5 nanograms?

A. Right.

Q. Right. And the other two on the first assay were slightly over .5 but on the second assay again dropped both of them to less than .5 nanograms?

A. Correct.

Q. Right. Now, in respect to the other ten patients in respect of whom one assay was run, can you tell me, without any inconvenience particularly, what the results of those recordings were?

Let me start this way. Were there



1
K-9 2 any readings on those ten patients that were in
3 excess of .5?

4 A. No, there were none over .5.

5 Q. All right. And when you
6 previously told me, Dr. Soldin, that in respect of
7 the group of six that a second assay was run on
8 different samples - I'm sorry, a second assay was
9 run on different samples, were they, and I may
10 have asked you this and if I did please forgive me,
11 were they the same kinds of samples, i.e., plasma
12 or serum as had been applicable on the first
instance?

13 A. Right, right.

14 Q. Right. Are you familiar, Dr.
15 Soldin, with the report prepared by the Dubin
16 Review Committee with respect to the Hospital for
17 Sick Children released in January of 1983?

18 A. I've read most of that.

19 Q. Are you familiar, sir, with
20 that portion of the report which speaks about the
21 events that occurred in January of 1982 on Ward 7F
22 of the Hospital?

23 A. Right.

24 Q. Perhaps your counsel could
25 get you that.



K-10

1 I draw your attention to page 178,
2 sir.

3 THE COMMISSIONER: Unfortunately,
4 I left it and I asked the poor fellow to go and
5 get the Dublin Report, forgetting that there is
6 nothing about Dublin on the front of it at all.

7 MS. CRONK: Q. I draw your
8 attention, Dr. Soldin, to page 178 of the report
9 if I could.

10 A. Right.

11 Q. In that section of the report,
12 the illness of these five children that you have
13 described to us this morning is also described, and
14 with respect to the child upon whom a 1.3 digoxin
15 recording was made, it is suggested that that
16 reading was the result of an error in drug
17 administration, that is, it is suggested that there
18 was a medication error and digoxin was prescribed
19 to that child when it was intended for another
20 child. Can you help me, sir, as to whether, as
21 the person who supervised these tests, you have
22 any knowledge as to whether that 1.3 reading
23 occurred as a result of a medication error, as
24 suggested in this portion of the report?

25 A. No. It could have been as a



K-11

1

2

3

4

result of the medication error, but it need not necessarily have been as a result of a medication error.

5

Q. Are you satisfied, sir, that it was, or do you have any knowledge as to that?

6

A. No. I think that in the

7

light of information which we have today that it could well be that that was not as a result of the medication error.

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. And if we take for the moment, make the assumption for the moment, I'm not suggesting it is in fact what happened, but if we take the assumption for the moment that it was a medication error, I take it that the highest result that was recorded, or the highest digoxin reading that was recorded for any of these 15 patients was a 0.8 which, on a second assay, was reduced to 0.4 ---

THE COMMISSIONER: I'm sorry, I don't understand what you're saying.

MS. CRONK: I'm sorry.

THE COMMISSIONER: Assuming that it was a ---

MS. CRONK: If we assume that the 1.3 digoxin reading related to a patient who had in



K-12

1

2 fact been administered digoxin ---

3 THE COMMISSIONER: Oh, I see, yes.

4 The highest would be 0.8, yes. Yes, I think that
5 speaks for itself.

6 MS. CRONK: Q. Now, in respect of
7 all of these tests, both the first and second assays
8 conducted on the group of six children, and the one
9 assay run in duplicate on the other children, were
all of those samples antimortem samples, Dr. Soldin?

10 A. Yes, they were.

11 Q. And did the Hospital identify,
12 in the case of the five or six children who became
13 ill, some cause thought to have resulted in the
similar illness?

14 A. Yes, they did.

15 Q. And what was that, sir?

16 A. They thought that these
17 children had received epinephrine instead of vitamin E.

18 THE COMMISSIONER: I'm sorry, that
19 they had received what?

20 THE WITNESS: Epinephrine.

21 THE COMMISSIONER: Oh, yes, instead
of vitamin E.

22 THE WITNESS: Yes.

23 THE COMMISSIONER: That's the Murphy

24

25



1

K-13 2 child, was it, that died?

3

THE WITNESS: Right.

4

5

6

7

in supervising the conduct of these tests, run a test for cross-reactivity between epinephrine and the antibody on the RIA methodology that was being used?

8

9

A. Yes, we ran cross-reactivity studies on epinephrine and on vitamin E.

10

Q. And on vitamin E?

11

A. Right.

12

Q. With what results, Dr. Soldin?

13

A. There was no cross-reactivity, measurable cross-reactivity.

14

Q. For either?

15

A. For either.

16

17

18

19

20

21

22

23

24

25

Q. Right, thank you. Now, after the tests that were conducted in January of 1982, did you have occasion later in that year, Dr. Soldin, to run digoxin assays on any other patients who were known not to have been prescribed digoxin?

A. Yes, we did. We were

interested of course in obtaining values that were greater than .2 in many of these children that were not receiving digoxin. So, we asked our neonatal



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin, dr.ex.
(Cronk)

1333

K-14

1
2 ward to, whenever they could, send us a sample,
3 to send us samples for digoxin analysis on patients
4 not receiving digoxin. Three such samples were
5 obtained during '82 and the results on all three
6 were less than .5.

7 Q. And in respect for those
8 samples, Dr. Soldin, do I take it that those were
9 all ante mortem samples as well?

10 A. They were ante mortem samples,
11 right.

12 Q. And they were as well plasma
13 or serum?

14 A. Right.
15 -----
16
17
18
19
20
21
22
23
24
25



6jul83

L
DMra

1

Q. And because it was 1982, are we talking about the RIA methodology as having been employed for those tests, or were any of the three or all of the three conducted on FPIA during the month it was there for evaluation purposes?

6

A. The RIA methodology.

7

THE COMMISSIONER: I'm sorry, what was that?

9

THE WITNESS: RIA methodology.

10

MS. CRONK: Q. And at the time these tests were conducted, Dr. Soldin, did you have any knowledge or understanding as to whether any of the three patients suffered from cardiac ailments?

14

A. No, I didn't. The way the study was set up was in a blind fashion. In other words, we were supposed to receive samples without knowing whether or not those patients were on digoxin.

15

Q. I see.

16

A. So, that is the way it was set up. We had no knowledge.

17

THE COMMISSIONER: You said these readings were less than what?

22

THE WITNESS: 0.5.

23

MS. CRONK: Q. That is nanograms

24

25



1

L2 2 per ml?

3 A. Right.

4 Q. And similarly, when you indicated they were to be conducted in a blind fashion,
5 do I take that to mean that you were, as well, not
6 provided with particulars concerning their clinical
7 condition?

8 A. Correct.

9 Q. And that would apply as well
10 to kidney problems as well as to cardiac problems?

11 A. Any problems. Those samples
12 came down to the laboratory in the exact same
13 fashion that any other samples would come down,
14 with a requisition saying they wanted a digoxin
sample assay.

15 Q. And did you, after conducting
16 the tests, determine whether or not any of those
17 children had been on a prescribed digoxin level?

18 A. I have had verbal communica-
19 tions with doctors on 7G, yes, which indicated to
20 me that those were the only three samples they sent
down to us during 1982 in this study.

21 Q. And were any of those three
22 patients on prescribed levels of digoxin?

23 A. No, they were not on digoxin.

24

25



L3

1

Q. After 1982, doctor, dealing
with this year because we have heard evidence as
well as to the results of these tests on patients
who were not known to have been prescribed digoxin,
did you have occasion in 1983 to conduct digoxin
assays on patients who were known not to have re-
ceived digoxin?

2

A. Yes. We have been doing
that over the past ten days or so.

3

Q. Can you tell me, doctor,
how many patients have been sampled and tested?

4

A. Eight patients from our neo-
natal ward.

5

Q. Again, Ward 7F?

6

A. 7G.

7

Q. And what method was used for
the testing of those children's samples?

8

A. On all eight, the FPIA method
was used and, on five of those eight, the RIA method
was used.

9

THE COMMISSIONER: I'm sorry. You
said the FPIA on three; is that right?

10

THE WITNESS: The FPIA method was used
on all eight and the RIA method was used on five of
the eight. In other words, the exact same samples

11

12



Soldin
dr.ex. (Cronk)

1

L4 2 were analyzed by both methods.

3

MS. CRONK: Q. We are talking now
of tests that have been conducted on eight children
in total within the last ten days in your laboratory --

4

THE COMMISSIONER: I am being very
slow on this. What did you say, on all eight of
them, you conducted the new method?

5

THE WITNESS: Correct.

6

THE COMMISSIONER: What you call
the FPIA; is that right?

7

THE WITNESS: Right.

8

THE COMMISSIONER: Yes. All right.

9

MS. CRONK: Q. -- and you used, as
I understood it, you just told the Commissioner, Dr.
Soldin, the same sample for five of those patients
to run a second test on the RIA method in addition
to the test or assay that you were running on the
new method, the FPIA; is that correct?

10

A. Right.

11

Q. And we are talking eight
children in total?

12

A. Eight children in total.

13

Q. Can you tell me, sir, or do
you know what the approximate ages of those children
were?

14

15



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

1338

Soldin
dr.ex. (Cronk)

L5

A. Again, under two months.

Q. And what kind of samples were obtained?

A. Serum or plasma.

Q. Are we talking about ante mortem samples or post mortem?

A. Ante mortem samples.

Q. And what were the results, first, Dr. Soldin, dealing with the five assay tests done on the five children by the RIA method?

A. One result was over 0.5, four of them were below 0.5. The one that was over, was 1.4.

Q. I'm sorry?

A. Nanograms per ml.

Q. Let's go through that again, Dr. Soldin, if we could.

Of the five tests that were conducted on the RIA method, I understood you to say that four readings were less than 0.5 nanograms per ml; is that correct?

A. Correct.

Q. And one reading was 1.4 nanograms per ml?

A. Correct.



L6 1
2 Q. And that is the only one of
3 that group of five on the RIA method that was over
4 .5 nanograms?

5 A. That's right.

6 Q. Now, let's deal with the FPIA
7 test results on all eight children.

8 Can you tell us what the recorded
9 levels were there?

10 A. Seven of the eight were less
11 than 0.5 and one was 0.9 nanograms per ml.

12 Q. 0.9?

13 A. Correct.

14 Q. And was the child, Dr. Soldin,
15 the sample that recorded 0.9 on the FPIA, the same
16 child that recorded 1.4 on the RIA?

17 A. Yes.

18 Q. So I take it, at least in
19 respect of that sample, the FPIA reading was lower
20 than the RIA reading?

21 A. That is right.

22 Q. And to what, if anything, can
23 you presently attribute that, Dr. Soldin?

24 A. Well, there are several
25 possibilities. One is that the antibody is more
specific, the antibody used by the FPIA procedure,



1

L7

2

more specific with respect to whatever compound is
being measured.

4

Another possibility is that, because
we are deproteinizing in the FPIA method, we are
deproteinizing - in other words, we are removing
the proteins --

7

Q. Thank you.

8

A. -- we may be removing a
compound that cross-reacts with the antibody and
you wouldn't measure that by the FPIA method because
we have no proteins there.

11

12

Q. But you would measure it with
the RIA method?

13

A. But you might measure it, right.

14

15

Q. Now, am I correct, Dr. Soldin,
that in respect of all these eight children, in all
of these test results, taking into account even
the highest - which was the 1.4 on the RIA and
the same child being the .9 on the FPIA - that all
of those recorded readings are within what would be
considered the therapeutic range for digoxin had
it been administered?

21

22

A. No. The therapeutic range
is 0.8 to 2.0 nanograms per ml.

23

Q. That's right.

24

25



L8 2 A. And a lot of these kids had
3 values below 0.5; so, they were outside the thera-
4 peutic range.

5 THE COMMISSIONER: They were sub --

6 MS. CRONK: I'm sorry.

7 Q. They were sub-therapeutic
8 or within the therapeutic range.

9 A. Right.

10 Q. And that would apply as well
11 to the tests that were conducted that you described
12 a few moments ago in 1982 on the three patients
13 sampled?

14 A. Yes.

15 Q. And, as well, it would apply
16 to the test results in January of 1982?

17 A. That is correct.

18 THE COMMISSIONER: There was one at
19 2.1 - it is all a matter of record.

20 THE WITNESS: That's right.

21 THE COMMISSIONER: The 2.1, it
22 depends on what standards you use. If you use 2.0
23 as the limit of the therapeutic range...

24 MS. CRONK: Q. The 2.1, as I
25 understand it, was indeed in respect of a child who
 had been prescribed digoxin, and you are quite right,



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin
dr.ex. (Cronk)

1342

1

L9 2 in the range that you have described, Dr. Soldin,
3 that would be slightly above the therapeutic range.

A. Right.

5 Q. That is the one that was
also reduced on the second assay?

A. Right.

Q. Now, all of these tests and assays, as I understand it, Dr. Soldin, were conducted on ante mortem samples, all of them?

A. That is right, yes.

11 Q. Now, as I understand it, there
12 have, in fact, been - and please correct me if I am
13 wrong - post mortem sampling or assays done for
digoxin in the Hospital since March of 1981?

14 A Yes

Q. And have some of those assays been conducted in your laboratory?

A. Yes, they have.

Q. At whose request were those particular samples analyzed, those assays undertaken?

20 A. At the request of the pathologist.

Q. And was that more than one
pathologist or are we talking about one doctor
specifically?

24

25



L10

1

2 THE COMMISSIONER: I thought it was
3 a matter of routine. Am I wrong about that?

4

MS. CRONK: That is what I am coming
to, Mr. Commissioner.

5

Q. Were these assays conducted
at the request of one particular pathologist at the
Hospital or a number, as a matter of routine?

6

A. It became a matter of routine,
I think, after March of 1981, to measure digoxin
in all autopsy samples if the samples came to us,
obviously, from the Pathology Department.

7

Q. Perhaps my understanding is
incorrect. Did they come to you from any particular
doctor or pathologist?

8

A. From a number of doctors.

9

Q. Now, when I asked you, Dr.
Soldin, whether those tests were conducted from
March of 1981 forward, are they still being con-
ducted as at today's date?

10

A. That is correct.

11

Q. And were any of those tests or
assays, in fact, undertaken in the latter part of
March of 1981?

12

A. I think they were, yes.

13

MS. CRONK: Mr. Commissioner, as you

14

15



1

L11 2 might anticipate, I have had an opportunity to
3 discuss this particular matter with Dr. Soldin before
4 he came today to give evidence.

5

6

7

8

9

It is the proposal of Commission
Counsel that Dr. Soldin, or Dr. Phillips, a Patholo-
gist from the Hospital For Sick Children, will be
called to give evidence in detail regarding both
the conduct of these post mortem assays for digoxin
and as to the test results realized.

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

The reason for that is that it is
Commission Counsel's understanding that many of
these post mortem tests, in fact, coincide with
the month of March 1981 and several of the children
with whom, sir, you are concerned in the inquiry
period and, rather than deal with those at this
stage, we propose to deal with all of the post
mortem digoxin assay tests on children known not to
have received digoxin in one grouping through one
witness at a later date.

THE COMMISSIONER: Yes. All right.

26

27

28

29

30

31

32

33

34

35

It becomes a very fine line, of course, because we
want to know, I would think, in this part of the
inquiry just what the results were generally.

Can we not ask a question to know
generally what was the highest - We all know about



1

L12 2 Baby Murphy, that there was an inquest a little
3 while ago - what was the general range, the highest
4 range that you obtained.

5 MS. CRONK: Sir, I don't mean to
6 interject, and please excuse me. Some of the
7 ranges that I understand will be given to you in
8 response to that question are, indeed, what have
9 been perceived to be the very high ranges on the
children that were tested in March of 1981.

10 I understood from Dr. Soldin that he
11 would have difficulty on this particular day in
12 telling us, for example, what the highest was on
children outside the March 1981 time period.
13

14 If I am wrong, Dr. Soldin...

15 I am entirely in your hands, Mr.
16 Commissioner. If you would like that evidence led
now, I am prepared to do so.

17 THE COMMISSIONER: Obviously, you
18 don't want that, so I am not going to press it.

19 MR. STRATHY: If I might make one
20 observation and that is as it relates to the FPIA
21 method. It had been my understanding that Dr. Soldin
22 had used FPIA on autopsy samples and that one of the
23 factors influencing his views on FPIA was the results
on autopsy samples, or at least that was my under-
24
25



L13 1 standing. He might be able to give his evidence
2 on autopsy samples on FPIA.

4 THE COMMISSIONER: It is going to
5 be very difficult then, Miss Cronk, to keep this
6 out. Is there not some kind of a chart that we have?
7 Not the babies which we are inquiring about, but the
8 other babies? The other babies are regular post
9 mortem examinations. Those figures are not available,
I take it?

10 MS. CRONK: Well, the difficulty, as
11 I understand it, sir - and, again, if Dr. Soldin
12 has the information today and is in a position to
13 provide it for us, I have no difficulty in exploring
14 that area. My understanding was, though, that many
15 of these assays were undertaken at the request of
16 Dr. Phillips, the Pathologist at the Hospital, and
17 that Dr. Phillips was the appropriate individual
18 to give evidence concerning the results as a whole.

19 If my understanding in that regard
20 is mistaken, we can deal with those autopsy results
21 right now.

22 THE COMMISSIONER: Well I don't know
23 what sort of a task it is. Is it going to take hours
24 to get it or is it just going to take minutes.
25 What is it?



L14

1

MS. CRONK: Well, Mr. Commissioner,
in any event, it was going to be my suggestion that,
when we break for the noon break, with Miss Devin's
concurrence - and I don't have prior authority for
this, but with her concurrence and Dr. Soldin's
willingness that Dr. Soldin make himself available
at this stage for various questions from other
counsel.

9

THE COMMISSIONER: That's fine.

10

MS. CRONK: And we can perhaps ex-
plore this issue then.

11

12

THE COMMISSIONER: You are now, as
plotted; you are finished?

13

14

15

16

17

18

19

20

21

22

23

24

25

RCHSC
July 6



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin, dr.ex.
(Cronk)

1348

DM.jc
M

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

MS. CRONK: There is one small area, about five minutes, Mr. Commissioner, and I propose to deal specifically - if we could I suggest we break now and let other counsel have the benefit of learning from Dr. Soldin what I have learned about these autopsies.

THE COMMISSIONER: Could we just know what this small area is?

MS. CRONK: I am sorry. The only area left that I intend to explore with Dr. Soldin relates to recovery rate studies that he has conducted in respect to the RIA tests at the Hospital, and the FPIA tests.

THE COMMISSIONER: Yes, all right.
Yes, Mr. Buhr?

MR. BUHR: Could I just interject, Mr. Commissioner. I assume from Dr. Soldin's evidence that the major reason for this whole testimony about the FPIA and clearly he has already indicated that one of his concerns is from the results of these autopsy reports so hopefully I would ask that the Doctor acquaint himself with these studies over the lunch period because it makes it very difficult to cross-examine him on that area at all if he is not really up to date on it.



M.2

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

MS. CRONK: I think perhaps, Mr. Commissioner, we can resolve the issue this way. We know that the FPIA methodology has only been in use in the Hospital on a full-time basis since March of this year. Perhaps I can direct Dr. Soldin's attention to the particular autopsy --

THE COMMISSIONER: That is not what is worrying me and I do not think it is what is worrying anybody else. It is that this, presumably, from the routine post mortem examinations of these babies who died, you cannot have a post mortem examination unless the baby did die, there are figures available as to the digoxin levels. That is surely what we want to know. These are not the babies who are under inquiry now. Now, if you do not want to give it to us I suppose I can play the game and forbid the cross-examination, but it seems to me that that would be most important.

MS. CRONK: It is not a question at all of not wanting to provide it, Mr. Commissioner. I had understood that Dr. Soldin did not have those full figures available today and what I would propose to do, if it would at least resolve some of my friends' dilemma, so that they could have a full and complete cross-examination of Dr. Soldin with respect



M.3

1

2 to this particular methodology, is to ask him to
3 acquaint himself over the noon hour, if he does not
4 have it already, with those autopsy post mortem
5 sampling results that he looks to in support of
6 his judgment as to the efficacy and desirability of
7 the FPIA test, if that can be done.

8

THE COMMISSIONER: I don't know, can
it be done, Doctor?

9

10

11

THE WITNESS: I have the data here
with regard to the FPIA tests and I could talk about
it right now if you wish.

12

13

14

THE COMMISSIONER: Have you got the
figures? Have you got the figures for the routine
post mortem examinations for digoxin after March of
1981?

15

16

THE WITNESS: I do not have all the
figures.

17

18

THE COMMISSIONER: Just a minute. Yes,
Mr. Bogart?

19

20

21

22

23

24

MR. BOGART: I do not know if this is
helpful, Mr. Commissioner, but I am trying to be
helpful. At least in respect to readings in excess
of 5 on autopsy samples taken since March of 1981,
I believe that is contained in Volume 13 of Dr. Ellis'
testimony at the preliminary inquiry, starting at
page 12.

25



M.4

1

2

3

4

If that will help Dr. Soldin and
Miss Cronk, I simply raise that for that purpose. You
remember I referred to that yesterday.

THE COMMISSIONER: Yes. I think what
we might do, what about your considering this
problem. It is a matter of considerable interest and
I do not see why that is not included in this aspect
of the Inquiry because it does not involve these
particular children. When we do get to the particular
children we want to know what the readings were with
other children who have died since that time and for
which there is no suspicion of foul play.

MS. CRONK: I quite agree, Mr.
Commissioner, and if Dr. Soldin has that information
available --

THE COMMISSIONER: Do you want to see
if you can get that? Now, the other thing I was
wondering is about - you have not consulted with him
yet or with his Counsel. Who is acting - what is
your position with regard to --

MS. DEVINS: I am acting and will
be acting for Dr. Soldin.

THE COMMISSIONER: Would you consult
with him and determine whether he is willing, after
the examination is completed, I think we will come

24

25



M.5

1

2 back here at 2:30 to complete the examination and
3 then perhaps we might, I don't know, we will decide
4 then whether we will take the rest of the afternoon,
5 if Dr. Soldin is willing, for the informal examination,
6 or whether we will start the cross-examination later
on this afternoon.

7

MS. DEVINS: Fine, Mr. Commissioner.

8

MR. BOGART: Sir, can I ask one more
9 thing?

10

THE COMMISSIONER: Yes.

11

12 MR. BOGART: This is the point I
13 raised yesterday with respect to the transcripts of
14 Dr. Ellis, Volume 13, beginning at page 12, my under-
15 standing is there are also some reports in respect
16 of ante mortem readings in excess of 5. I believe
17 that to the extent that we would be interested in
18 autopsy --

19

20 THE COMMISSIONER: But the routine
21 examination was post mortem. There was no routine
22 ante mortem examination.

23

24 MR. BOGART: That is what I was not
25 clear about yesterday, sir. My understanding from
the transcript is that there were over 3,000 of these
tests done.



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin, dr.ex.
(Cronk)

1353

M.6.

1

2 I am just raising that, sir, because
3 if you deem it relevant at this point I would like to
4 ask some questions about it. If it is not relevant
5 at this point, I will ask them later.

6

THE COMMISSIONER: Well, let us see
what we come up with at 2:30.

7

8

---- Luncheon adjournment.

9

10

11

12

13

14

-

15

16

17

18

19

20

21

22

23

24

25



AA/DP/ak

1

2

---Upon resuming at 2:30 p.m.

3

THE COMMISSIONER: Yes, Ms. Cronk.

4

5

6

7

8

9

MS. CRONK: Q. Dr. Soldin, you will recall before the break we were discussing a series of ante mortem samples that had been taken from patients known not to have received digoxin and in respect of which digoxin assays had been run. Do you recall that discussion?

10

A. Right.

11

12

13

Q. I would like to talk for a moment about the ante mortem testing results that we were discussing earlier and then I will return to the post mortem testing.

14

15

16

You told us this morning that they were, as I understood it, five samples tested on both the RIA and the FPIA method. Is that correct?

17

A. Correct, yes.

18

19

20

21

Q. Can you tell us, because you gave us the recorded levels of those tests, can you tell us whether the levels recorded were lower pursuant to one technique versus the other on those five samples?

22

23

A. The results were lower by the FPIA method.

24

25

Q. Are you able today, sir,



1

2

to give us a breakdown as to what the results were
by FPIA versus RIA?

4

5

6

A. I do not have those numbers
here but I could certainly get them. The mean
result was definitely lower by the FPIA method.

7

Q. On all five?

8

A. The mean result. I think all
five were lower, yes.

9

10

11

Q. As I understand it, you do not
have a particular breakdown with you today but you
will provide it to us?

12

A. Certainly.

13

Q. Thank you.

14

15

16

17

18

19

Can you tell, Dr. Soldin, were those
five samples that we have talked about the only
ante mortem samples from patients known not to have
received digoxin which were available to you for
comparative testing? In other words, are they the
only ones on which you have run tests both on the
RIA and the FPIA, ante mortem?

20

21

A. The patients who were not on
digoxin, you mean?

22

Q. Yes.

23

A. They were the only ones that
I currently have a comparison of the two techniques.

24

25



1

2

Q. Again, those samples related
to patients known not to be on digoxin?

3

A. Correct.

4

Q. Have you had occasion since the
introduction of the FPIA technique to the Hospital
in March of this year to do a comparative study run,
if I can express it that way, on ante mortem samples
of patients known to be receiving digoxin?

5

A. Yes, I have.

6

Q. Can you tell me, first,

7

Dr. Soldin, how large that sample group was?

8

A. There were 36 samples in that
group. Both the RIA and the FPIA methods were
used. Comparison data is summarized in a memo
that I sent to Dr. MacLeod on the 15th of June.

9

Q. 15th of June of this year?

10

A. Of this year.

11

Q. I have the memorandum in front
of me, Dr. Soldin, which is dated June the 15th,
1983 expressed to be from yourself to Dr. MacLeod,
Clinical Pharmacology, on the subject of digoxin
measurements.

12

Is that the memorandum to which you
were just referring?

13

A. It is, yes.

14

15



1

2

MS. CRONK: Could that be marked,
sir, as the next exhibit, please?

4

THE COMMISSIONER: Exhibit 25.

5

---EXHIBIT NO. 25: Memo from Dr. Soldin to
Dr. MacLeod dated June
15th, 1983 re Digoxin
Measurements.

7

8 MS. CRONK: Q. In respect of
9 those 36 samples, Dr. Soldin, were the same samples
10 tested on both the RIA and the FPIA techniques?

11

A. They were, yes.

12

Q. What type of samples were they?

13

We know that they were ante mortem samples, but
were they whole blood, plasma ---

14

15

A. They were serum or plasma

samples.

16

17

18

Q. Are you in a position to
describe for the Commissioner what the comparative
results were in respect of those samples on both
methodologies?

19

20

21

22

23

24

A. The methods compared exceedingly
well in that study. The mean results by the RIA
method expressed in nanograms per millilitre was
1.19. The mean results by the FPIA expressed in
nanograms per millilitre was 1.15. The results in
the actual memo were in nanomoles per litre.

25



1

2

Q. Where do we find that in the
memorandum, Dr. Soldin?

4

5

A. It is on the second page, at
the top of the page.

6

7

Q. There are three sections of
tabular results on this page - those on the top.

8

9

A. Right.

Q. And they are there expressed,
I believe you said in nanomoles.

10

11

A. As typed, yes, in nanomoles,
and I have converted them into nanograms for you.

12

13

Q. So the RIA mean result shown
as 1.53 would be in nanomoles, which you refer to
as 1.19. Correct?

14

15

A. Correct, 1.19 nanograms.

Q. And similarly the mean result

16

17

18

19

20

on which you have described here as TDX, and I
take that to be the FPIA method, is expressed in
nanomoles at 1.48 and converted to nanograms -
that would be, I think my notes says that you said
1.15 nanograms?

21

A. Right.

22

Q. Can you help us today,

23

Dr. Soldin, as to whether or not ---

24

THE COMMISSIONER: Sorry, I'm

25



1

2

having trouble. 1.53 for ---

3

MS. CRONK: The RIA.

4

THE COMMISSIONER: Yes, and 1.48?

5

MS. CRONK: The TDX.

6

THE COMMISSIONER: If we do this

7

in nanograms it is ---

8

MS. CRONK: 1.19 for the RIA.

9

THE COMMISSIONER: 1.19 - oh, I see,
now it makes sense. Thank you.

10

MS. CRONK: You are welcome.

11

Q. Can you help us today,

12

Dr. Soldin, with whether or not the patients from
whom these 36 samples were drawn were all of the
same age group or age range, or do you know?

13

A. No, it is exceedingly unlikely
that they were the same age group.

14

Q. Were any of them neonates?

15

A. I cannot tell you. I would
doubt that, because we needed quite a lot of samples.

16

Q. Were all of these samples
tested in your laboratory, Dr. Soldin?

17

A. They were tested in our
laboratory, yes.

18

19

20

21

22

23

24

25



6jul83
BB
BMcra

1

Q. All right.

2

And can you tell me, of the 36 samples tested by both methods, what was the highest reading which you obtained on the RIA method?

3

A. The highest reading was 2.3 nanograms per millilitre. Again, in the graph it is in nanomoles per litre; so, it is a bit confusing.

4

Q. Where is that shown on the graph?

5

A. It is page 3.

6

Q. That is the graph where various items are plotted with RIA shown on the bottom axis of the graph?

7

A. Yes.

8

Q. And what is shown on the left-hand side of the graph?

9

A. The FPIA method.

10

Q. All right.

11

So that the highest reading on RIA that you obtained was 2.3 nanograms per millilitre?

12

A. Right.

13

Q. What was the highest FPIA result that you obtained?

14

A. It was 2.2 nanograms per millilitre.

15

16



BB2

Q. Well, can you explain for us,
Dr. Soldin - or do I take it correctly that the
graph, which is page 3 of this memorandum, is a
plotted reflection of the results that you obtained
by both methods on these 36 samples?

A. That's right.

THE COMMISSIONER: I guess that's
clear. The one I'm looking at seems to have all
sorts of axes up around the --

THE WITNESS: Each axis represents a
sample, yes.

MS. CRONK: Q. Can you tell us,
Dr. Soldin, how we distinguish on this graph between
an RIA tested sample and an FPIA tested sample?

A. Well, each sample was tested
by both methods. You then plot the value you get
on the RIA axis versus the value you get on the FPIA
axis.

Q. And there appears to be a
dotted dividing line or an axis through the graph.

Are the axes which appear below it
the RIA results?

A. No, no. All of the results
plotted have been done by both methods.

Q. Yes.



BB3

-1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

A. And we then plot the axes and then you work out by what is the best fitted line to this, to these series of plots.

Q. All right.

Well, in looking at this graph, if we wished to know the results obtained by the FPIA technique, how could we identify which were the FPIA results?

A. They would be on the left, on the left-hand side axis.

Q. All right. And the RIA on the right?

A. RIA on the bottom, right.

Q. All right. Thank you.

Now, returning to page 2 of the memorandum, Dr. Soldin, in tabular form --

THE COMMISSIONER: I don't know whether it matters but I am left completely in the dark with this graph. I just don't understand it at all.

The first thing you said, the highest that you got on the RIA is 2.3; is that what you said?

THE WITNESS: In nanograms, yes. The results are plotted in nanomoles. The Hospital switched to nanomoles on April 4th.

MS. CRONK: In an effort to make it



BB4

1

clearer, sir, I may have made it more confusing.

3

THE COMMISSIONER: No, no, you
didn't. But, sometimes, you have particularly dense
objects!

5

For the first time in my life, I have
sympathy for the anti-metric group!

7

This is -- it just makes it vastly
more difficult, but this thing is plotted in these
nanomoles?

10

THE WITNESS: Yes.

11

MS. CRONK: I asked Dr. Soldin for
what I hoped was the ease of reference to convert
the two highest readings into nanograms, and those
were, as I understand it, the 2.3 reading on the
RIA and the 2.3 on the FPIA.

15

16

17

18

Q. If we could turn then, Dr.
Soldin, to page 2 of the memorandum and the tabulated
results which appear in the middle section, could
you explain to us what the results reflect?

19

20

21

A. Well, both the middle and the
bottom section reflect the between-day precision
as obtained in our laboratory for both the RIA and
the FPIA methods.

22

23

Now, the FPIA is labelled as TDX
in this memorandum.

24

25



BB5

1
2 Q. And they relate as well to the
3 same 36 samples?
4

5 A. No, no. These are between-day
6 precision studies. These 36 samples were not
7 analyzed every day for twenty days, but different
8 quality control materials were analyzed every day
for twenty days and for nineteen days with the FPIA
method, as you can see.

9 n=20 means that they were assayed
10 20 times once a day for twenty days. n=19 means
11 they were assayed once a day for nineteen days, and
12 the mean results are shown again in nanomoles per
13 litre for these three different quality control
14 serums, and you can see that the results are fairly
close for the RIA and for the TDX or FPIA method.

15 The precision data again reveals
16 that what we have plotted here is a coefficient
17 of variations, which is a measure of the precision.

18 If you want me to go into more depth
19 on that, I would be happy to do that.

20 Q. Well, all right. Let me deal
21 with this for a moment.

22 What does the data shown in that part
23 of the table, that is, the second tabular section,
24 indicate to you in respect of the FPIA method versus

25



BB6

1

the RIA method? What does it tell you?

2

A. In the second section, it tells me that the precision of the two procedures is comparable at three different concentrations of digoxin and that the accuracy of the method at those three concentrations is also comparable.

3

Q. And the lower section of the tabulated result in the bottom of that page?

4

A. That was another precision between that precision study, again, at three different concentrations and, really, the interpretation of that table is the same as the middle.

5

Q. So that the precision of both methods on these studies was very close to each other?

6

A. Right.

7

Q. Now, leaving aside for the moment, Dr. Soldin - and I will return to this memorandum - the question of ante mortem samples. Turning now to post mortem samples. Since the introduction of the FPIA methodology in the Hospital in March of this year, have you had occasion to do comparative testing on post mortem samples for digoxin on both the FPIA and the RIA methods?

8

A. Yes, I have.

9

10



BB7

Q. And how large was the sample group you have used for those purposes?

A. I am just trying to find it.

Q. That's fine.

A. I believe we have analyzed 37 samples by both procedures, autopsy samples.

Q. They were all autopsy samples?

A. Is that not what you asked?

Q. Well, no, I used the word "post mortem". Were they all autopsy samples?

A. They were, as far as I know, yes.

Q. And were these samples again plasma or serum?

A. Correct.

Q. And the same samples, that is, all 37, I take it, were tested on both the RIA and the FPIA?

A. They were.

Q. Can you help us as to whether or not the patients from whom these samples were taken had been or had not been on prescribed doses of digoxin?

A. Well, some had been and some had not been, and I can't -- I don't have that

24

25



BB8 1 tabulated. I don't know. May I refer you to Dr. Phillips, who has all the data on autopsy samples.

Q. 2 Well, will Dr. Phillips be able 3 to tell us how many of the sample group were patients 4 that were on prescribed levels of digoxin?

A. 5 He should be able to, yes. 6
He has that data.

Q. 7 All right. 8
And can you help us today, Dr. Soldin. 9
Do you know, sitting here today, or in the papers 10
that you have with you today, the sites in the body 11
from which these 37 samples were taken? 12

A. 13 No, I don't.

Q. 14 And who would be the appropriate 15 individual?

A. 16 Dr. Phillips is the person.

Q. 17 Dr. Phillips?

A. 18 Yes.

Q. 19 Can you tell us again today 20 from the information you have on hand or that you 21 know how soon after death these 37 samples were taken?

A. 22 No.

Let me make it clear. Our laboratory 23 gets autopsy samples which are just numbered and, 24 mostly, we do not get names; we get just a number,

25



BB9

1

2 autopsy number so and so, and then we handle the
3 analysis and then report the results to Dr. Phillips.
4 So, he has essentially all the data. He collects
5 the data, but we don't.

6

Q. Do I take it then that Dr. Phillips compiled the summary data of the results of all of these tests?

7

8

9

10

11

A. Well, he has a summary of all the autopsy results. I'm not sure whether he has the fluorescence polarization results on the autopsy samples.

12

Q. All right.

13

A. Because that was a study which we initiated.

14

15

16

17

18

19

Q. Well, are you then, Dr. Soldin, as the biochemist who is overseeing the use of that methodology, are you then in a position today to give us the breakdown of the results on those 37 samples; first on the RIA and then, comparatively, on the FPIA?

20

21

22

23

24

25

A. I can give you the following breakdown; namely, that, by both methods, there were 23 samples that had results of less than 0.5 nanograms per millilitre. There were three samples --



1

2

THE COMMISSIONER: That's less than
0.5?

3

THE WITNESS: Less than 0.5 for
4 both methods. There were three samples that had the
5 FPIA method - by the FPIA method, sorry, where less
6 than 0.5 but by the RIA method ---

7

THE COMMISSIONER: Take it slowly.
8 FPIA was 3 samples of less than 0.5. I take it those
9 are separate from the RIA ones, 3 that were only less
10 than 0.5 by FPIA, is that what you are saying?

11

THE WITNESS: No. Well, there were
12 23. I'm dividing it into separate groups. Now,
13 in the first group of 23 samples, both methods read
less than 0.5.

14

THE COMMISSIONER: I got 0.5.

15

THE WITNESS: Yes. In the second
16 group the RIA method read more than 0.5 and the FPIA
17 group method read less than 0.5.

18

THE COMMISSIONER: I'm sorry, you
will have to - it is partly the machine, but I'm
having trouble listening. The second group - could
you say that again?

21

THE WITNESS: The second group there
22 were 3 samples in which the FPIA method read less
23 than 0.5 nanograms per millilitre and the RIA method
read greater than 0.5.

25



BB2-2

jc

1

2

MS. CRONK: Q. On the same three
samples?

3

A. On the same three samples.

4

Q. Yes. That takes us up to 26.

5

What about the rest of the samples?

6

A. There were two samples in which
the FPIA method read greater than the RIA method.

7

Q. Yes.

8

A. And there were nine samples -- I
should qualify that further. Both of those two
samples had results greater than .5.

9

THE COMMISSIONER: Both of those what?

10

THE WITNESS: Would have results
greater than 0.5. So, there were two real readings
in other words of what were real measurements.

11

MS. CRONK: Q. But the FPIA results
were higher?

12

A. Yes.

13

THE COMMISSIONER: Wait a minute.

14

The FPIA were higher, is that not what you said?

15

THE WITNESS: In those two samples.

16

THE COMMISSIONER: Yes, all right.

17

Nine samples.

18

THE WITNESS: And there were nine
samples in which the RIA results were greater than
the FPIA result, again, greater than both methodologies

19



BB2.3

1

2 having resulted greater than 0.5.

3 MS. CRONK: Q. All right. Then
4 dealing, Dr. Soldin, with that last category, the
5 nine samples in respect of which the RIA reported
6 a higher result than was obtained on the FPIA. Can
7 you tell me of that nine what the highest two or three
RIA readings were that you obtained?

8 A. I believe the highest was 12.9
9 nanograms per millilitre.

10 Q. And how did that compare to the
11 FPIA reading on the same sample?

12 A. It was 7.4 nanograms per
13 millilitre.

14 Q. And for purposes of illustration,
15 which was the second highest RIA reading that you
obtained of those nine?

16

17

18

-

19

20

-

21

22

23

24

25



CC-1

DMeg

A. The second highest was actually on the same patient but drawn from another site. Now I would have to calculate the ---

Q. Well, what was the second highest on a different patient that you obtained on the RIA?

A. On a different patient it was 4.8 RIA nanograms per millilitre and 4.3 by FPIA.

Q. And I take it that inasmuch as you have told us that all nine of those samples had higher RIA readings and in the FPIA corresponding readings were lower, if we went to each of the nine we would just find a similar breakdown, the FPIA result would be lower than the nanogram measurement for the RIA?

A. That is correct.

Q. Now other than that sample group of 37 Dr. Soldin, since the introduction of the FPIA method at the Hospital, you have told us that was in March of 1983, have you had occasion to test any other post mortem samples on both methods for comparative purposes other than those 37?

A. No.

Q. Now looking at the results that you have described to us Dr. Soldin, and looking



CC-2

1

first, I am talking now about the comparative results that you have told us about. Looking first at the ante mortem tests done on patients who were not on digoxin, the five that were cross tested on both methodologies, and as I understand it you have told us that the FPIA results in those samples were lower than on the RIA?

A. That's right, yes.

Q. Now the next group of tests, that is the ante mortem samples from patients who were on digoxin were tested on both methodologies and the mean results as reflected in your memorandum I take it to be relatively the same?

A. Correct.

Q. And the third group of tests that you did on post mortem samples were done on both methods, were from patients who were both on prescribed doses of digoxin, and from patients who were not prescribed digoxin, correct? The ones you have just told us about.

A. The autopsy results?

Q. Yes, I'm sorry, the autopsy results, that is the group of 37?

A. That's right.

Q. And in those instances you have



CC2

1 told us that on at least 12 samples the results
2 obtained by the FPIA method were lower than the
3 comparative results on the RIA method?

4 A. Right.

5 Q. What do those results tell you
6 Dr. Soldin, if anything, about the comparative
7 advantages or disadvantages of both methodologies?

8 THE COMMISSIONER: Haven't told
9 him anything about the advantages, it would tell
10 him something about the readings, wouldn't it?

11 MS. CRONK: That would be fair, let
12 me rephrase it Mr. Commissioner.

13 Q. What do those results tell you
14 with respect to the reliability, or attractiveness
15 of one methodology for digoxin assays versus the
other, if anything?

16 THE COMMISSIONER: I still don't see
17 how the results can tell him. He may have some
18 opinion apart from that, or the results tell him
19 that either one is lower than the other, isn't that
right?

20 MS. CRONK: Well, you put it
21 fairly, Mr. Commissioner.

22 Q. Dr. Soldin, can you tell us,
23 have you formed an opinion with respect to these

24

25



CC4

1

2 methodologies on the basis of these comparative
3 studies that you undertook?

4 THE COMMISSIONER: If you have formed
5 any opinion other than the fact that one is lower
6 than the other I would be surprised, but perhaps
7 you have. On the basis of these figures I don't
8 know what conclusion you could possibly draw, but
there may be something else that you have.

9 THE WITNESS: Well the possible
10 conclusion that can be drawn is that if the FPIA
11 method may be somewhat more specific that is a
possible conclusion. The results, if we take the
12 patients that we know are not receiving digoxin and
the results were lower in the FPIA method, and in
13 the RIA method, that is a possible conclusion. I
think it is early in the use in our experience
14 with FPIA to draw a conclusion at this point in
time.

18 So again on the autopsy results
19 overall the FPIA results are lower than the RIA
results. In fact if you plot the nine samples in
20 which the FPIA results are lower than the RIA
results, you get a slope for that line of 0.6,
21 which means that the FPIA results tend to be 60 per
22 cent of the comparable RIA result.

24

25



CC-5

1 Q. Dr. Soldin ---

2
3 THE COMMISSIONER: May I just
4 quarrel with that finding with respect to the FPIA
5 being more specific. It certainly gets a lower
6 reading.

7 THE WITNESS: Yes.

8 THE COMMISSIONER: And you say
9 because they were not on digoxin, therefore there
10 should be no digoxin reading. We have been hearing
11 all sorts of evidence that in fact you can have
12 digoxin readings even if you haven't any digoxin in
13 your blood, because that is what the Vancouver study
14 was all about.

15 THE WITNESS: I know you can get
16 digoxin readings if you don't have digoxin in the
17 blood but that indicates a non-specific method for
18 digoxin.

19 THE COMMISSIONER: Either that or
20 it indicates some digoxin-like substance that
21 records on the RIA. I don't know, anyway that is
22 the conclusion you have reached?

23 THE WITNESS: Well, I would agree
24 with you it indicates that there could be a
25 digoxin-like substance that cross reacts with the
antibody. Another way of saying that in English is



CC-6

1
2 that the method is less specific. It is just using
3 your exact same words, am I not getting across to
4 you?

5 THE COMMISSIONER: No, no, you may
6 well be right. It gives you that comfort in any
7 event, does it, you think the FPIA more specifically
8 demonstrates and works better, and bearing in mind
9 that these children were not, did not have digoxin
prescribed for them?

10 THE WITNESS: There were only five
11 patients in which we have comparisons by both methods
12 in which digoxin was not prescribed, and the FPIA
result is lower than the RIA result in that group.

13 THE COMMISSIONER: I would accept
14 that conclusion if the FPIA method scored zero in
15 all instances for children with digoxin was not
16 prescribed. But if the FPIA method does produce
17 a reading of digoxin, where no digoxin has been
18 prescribed I have some difficulty coming to that
19 conclusion. That doesn't mean your reading of it
is better than mine. That is where the problem
20 is. If the FPIA came out with zero then I could
21 accept it, but because the FPIA reading comes out
22 with a figure which isn't zero doesn't it follow
23 that it might well be that the FPIA just doesn't

24
25



CC-7

1 pick up all the digoxin-like substances that this
2 substance X would be produced apparently in the body
3 of young children?

4 THE WITNESS: Yes, you are right,
5 conclusions are correct. It is not picking up as -
6 it is not measuring whatever compound you are
7 talking about whether it be substance X, that's ---

8 THE COMMISSIONER: It was measuring
9 something when nothing exists, wasn't it. However I
10 won't argue with you any more, probably clearly you
11 are more qualified than I am to reach a conclusion.
12 Anyway, that is your conclusion that the FPIA is
13 more specific?

14 THE WITNESS: My conclusion is a
15 guarded conclusion. We have little data at the
16 present time. We have those five patients that we
17 have done by both methods. We also have the
18 autopsy data from which we have done some 37 cases
19 by both methods, now many of the patients in the
autopsy study were on digoxin, right.

20 The FPIA method, taking both these
21 groups generally came out lower, the results by the
22 FPIA method, generally came out lower than the RIA
23 method and so a possible and in fact a probably
24 interpretation is that the FPIA method is more

25



Soldin, cr.ex.
(Cronk)

CC_8

1
2 specific.

3 MS. CRÖNK: Q. Dr. Soldin, you told
4 us earlier as well that you anticipate as a result of
5 active consideration of the matter by the Hospital
6 in the recent past that it is likely within two to
7 three weeks I believe that was the time frame that
8 you referred to, that all digoxin assays in the
9 Hospital would be done on the FPIA as opposed to the
RIA method. Do you recall giving that evidence?

10 A. Yes.

11 Q. And I take it that the
12 memorandum which you prepared for Dr. MacLeod and
13 which we have now marked as an exhibit is your
14 memorandum to Dr. MacLeod in support of that proposal?

15 A. That is correct. There was a
16 meeting held subsequent to that memo which was a
17 meeting with the Medical Director of the Hospital
18 and some of the administrators, et cetera. Dr.
19 MacLeod was there, and Dr. Goldberg was there, in
20 which the decision was made essentially to switch the
assay from the RIA procedure to the FPIA procedure.

21 This decision was made because of
22 the data that we had collected as well as because
23 of data that the AACC, that is the American
Association for Clinical Chemistry Therapeutic Drug

24
25



CC-9

1
2 Monitoring Program has published on the FPIA
3 procedure and how well that procedure is doing in
4 the external quality control programs relative to
5 other procedures.

6 Q. If we look at page 4 of the
7 memorandum and attachments that you forwarded to
8 Dr. MacLeod do we find in a typewritten form a
9 summary of what you consider to be some of the
10 advantages of moving exclusively to the FPIA
11 technique for running digoxin assays, together with
12 some of the disadvantages?

13 A. Yes, that's right, I have a
14 summary here.

15 Q. And when you refer in the
16 in the advantages section again, just for the
17 purposes of clarity to Stat - S-T-A-T - measurements
18 are you referring there to emergency or urgent
19 digoxin assay requests?

20 A. I am, yes.

21 Q. And if we look at the last page,
22 the last attachment to your memorandum Dr. Soldin,
23 can you explain to us briefly what this data
24 represents?

25 A. Basically this data is the
26 data for April of 1983 published by the American



CC-10 1
 Association for Clinical Chemistry and Therapeutic
 Drug Monitoring Program. There were 404 laboratories
 that performed digoxin assays in that particular
 month in this program.
5

6 Q. And do we find that indicated
close to the bottom of the page on the left beside
7 the words "all labs"?
8

9 A. Correct.
10

11 Q. All right.
12

13 A. There were some 312 in that
month that used the RIA technique, and there were
14 some 35 that used the fluorescence polarization-
immunoassay technique. You can see that the mean
15 results on this particular quality control sample
from both the RIA techniques and by the FPIA
16 techniques was the same.
17

18 Q. How do we see that Dr. Soldin?
19

20 A. Because under the column
"Mean" you get 3.87 for the RIA labs, that is 312
21 labs.
22

23 THE COMMISSIONER: I'm sorry, under
what column did you say?
24

25 THE WITNESS: The "Mean" column.
26

27 THE COMMISSIONER: Thank you.
28

29 THE WITNESS: The column is headed
30



ANGUS, STONEHOUSE & CO. LTD.
TORONTO, ONTARIO

Soldin, dr.ex.
(Cronk)

1382

CC-11

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

"Mean". You get 3.87 for the mean result obtained by the RIA laboratories, and you get 3.87 for the mean result for the FPIA laboratories. So the means were the same.

If you look at the standard deviations ---

Q. Which is the next column?

A. Which is the next column, the standard deviations reported by the RIA laboratories was 0.38 which is very close on a 10 per cent coefficient of variation, and the next column shows it was 9.78 per cent XC.V., so very close to 10 per cent.

In contrast the S.D. in the FPIA laboratories was 0.17 and the coefficient of variation was 4.43.

Q. Do I correctly take that to mean that on the basis of the experience on these laboratories, that is those who were using, during the month of April 1983 the RIA method and the FPIA method, that there was a greater variability results on the RIA assays than there were on the FPIA?

A. That is correct, from this data.



DP.jc
DD

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. What does the column headed what I take to be "minimum" and the column headed "maximum" indicate to us?

A. That should be the minimum result obtained and the maximum result obtained by all the labs for that particular type technique. So the minimum result obtained by the RIA labs was 0.42 on a sample that should have read around 3.8.

The target value, as you see in the far right-hand corner was 3.8.

Q. So we relate the figures in the minimum column to the target value of 3.8?

A. Correct. The target value was 3.8 and the mean result as obtained by the RIA labs was 3.87 which was pretty close to the target value but the worst laboratory had a result of 0.42, that is, the worst laboratory as far as being low is concerned; and the worst laboratory as far as reporting inaccurate high results was 11.79 so that the scatter as you can see - 3.8 was what they should have got but the scatter range from 0.4 to 11.79 in these 312 laboratories.

Q. If you take the 35 labs that use FPIA, the mean result was 3.87 which again was pretty close to the target of 3.80. The scatter



DD.2

1

2 was from 3.54 to 4.30 which I think you will agree
3 is a much narrower range and indicates a much
4 tighter control of the assay.

5 Q. And those values, I take it,
6 both in respect of the RIA results and the FPIA
7 results reflect a range of error or inaccuracy
8 reported on the assays conducted by that particular
9 technique in that month?

10 A. Right.

11 Q. And those factors as well - or
12 did they - have any relevance to your considerations
13 in preparing this proposal for Dr. MacLeod?

14 A. They had some relevance.

15 Obviously we cannot judge our RIA technique by the
16 results produced by other laboratories' RIA techniques
17 especially if their techniques are poor. So we have
18 to compare our precision by FPIA at Sick Children's
19 with our precision at Sick Children's using the RIA
20 technique, and those comparisons remain.

21 As you know, our RIA technique is
22 really quite a good technique and our CB's are very
23 comparable using the RIA technique to those obtained
24 by FPIA.

25 THE COMMISSIONER: Are you saying that
26 this is some kind of human error?



DD.3

1

2 THE WITNESS: It is error, whether
3 it is all human error is another issue. It could be -
4 there are a lot of reasons for a laboratory performing
5 poorly on a particular sample. Many of those reasons
6 are human errors.

7

8 These were assays done by 312 labs
9 all on the same sample, and it was sent to all these
10 laboratories and some of the labs using RIA techniques
11 perform very poorly. It could be that they were
12 using the wrong RIA kits or poor kits or poor anti-
13 bodies. There could be many reasons for producing
14 inaccurate results. The question one asks is are
15 those particular laboratories both inaccurate and
16 imprecise? I am talking about the labs that
17 performed poorly.

18

19 Q So that although there could be
20 many reasons leading up to a resulting range of that
21 kind it is the range of error or inaccuracy that is
22 at least one factor that you look to as a measure
23 of the efficiency of the particular technique?

24

25 A Right. What the study is showing
is that FPIA is such a simple technique, you can put
it in 35 labs and all 35 labs come out with data
which is almost the same, whereas the RIA technique
is perhaps a little more complicated and in some labs



DD.4

1

2 they perform well but in quite a few labs they do not.

3 MS. CRONK: Thank you, Dr. Soldin.

4 Mr. Commissioner, apropos of our
5 discussion before the break, I met with Dr. Soldin
6 and discussed with him, not in detail, the post mortem
7 testing samples that had been tested for digoxin
8 during the period March 1981 up to April of 1983,
9 that is all on the RIA method and not on the FPIA
method.

10 I am advised by Dr. Soldin and his
11 Counsel that the appropriate individual from whom
12 to obtain information as to the nature of the samples
13 tested and the results achieved is Dr. Phillips.

14 Dr. Soldin does have some limited,
15 with respect, some limited knowledge as to the results
16 of those tests and he is prepared to give it to us
17 today but he has cautioned me as has his Counsel
that --

18 THE COMMISSIONER: When is Dr. Phillips
19 scheduled?

20 MS. CRONK: Our hope would be to call
21 Dr. Phillips very close to the time that we intend to
22 recall Dr. Ellis because Dr. Ellis, as you know, will
23 be talking about specific sample testing that he did
24 and the results obtained during the July 1980 to

25



DD.5

-1

March, 1981 time frame.

2

It would then be our intention to call
3 Dr. Phillips to speak to those tests that were con-
ducted from March, 1981 until the introduction of the
4 FPIA method.

5

THE COMMISSIONER: In any event, I
6 take it, you are not going to ask him any questions?

7

MS. CRONK: That is not my intention,
8 sir.

9

THE COMMISSIONER: I suppose I do not
need to cross that bridge until somebody does.

10

MS. CRONK: I have no further questions
11 at this time of Dr. Soldin, Mr. Commissioner.

12

MR. STRATHY: Then I will raise the
bridge, Mr. Commissioner. It seems clear from the
13 witness' evidence that there are documents that
reflect the results of the various tests that have
14 been done.

15

THE COMMISSIONER: Are these the
post mortem results?

16

MR. STRATHY: I understand that they
are both pre-mortem and post mortem, from what
Dr. Soldin has said. I wonder if there is any
20 reason why those cannot be filed, if not today then
21 tomorrow, as exhibits?

22

MS. CRONK: I have no objection to
that at all, Mr. Commissioner. It is just that
in the time available there was not sufficient time
24 to copy much of that material.

25



DD.6

1

2

3

THE COMMISSIONER: Is there some
possibility we might have those tomorrow?

4

5

6

7

8

MS. CRONK: Yes, I will be glad to
undertake to meet with Dr. Soldin and arrange that.
I should make it clear however that the documents of
which I am aware, the documents that Dr. Soldin has
with him, relate to the comparative testing that
he conducted, that he has just described.

9

10

MR. STRATHY: I am not talking about
just those.

11

12

13

14

15

16

17

18

19

THE COMMISSIONER: If there are
documents available and if they can be produced, I
think it certainly would seem to me that that sort
of evidence is relevant, but there is no point in
having it if the witness does not know anything about
it. So I think counsel will just have to use their
discretion with respect to that. It is obvious that
if the witness does not know as much as he should
know about it to give any sensible answers then there
is not much point in pursuing it.

20

Is that the completion of your --

21

MS. CRONK: Yes, Mr. Commissioner. I

22

have spoken to Miss Devins, and Dr. Soldin, within
reason, is willing to meet with other counsel, if it
will assist them in preparing their cross-examination.

23

24

25



DD.7

1

2

THE COMMISSIONER: What is the
general feeling? Would you prefer to have that
sort of session now? If we have that sort of session
now we may as well adjourn until tomorrow morning.
If, on the other hand, if anybody wants to cross-
examine now we will do it that way.

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Can we have a sort of a show of hands,
if you like, as to who wants to have the informal
discussion with Dr. Soldin now? Can we have a show
of hands? It looks as though that is fairly well
unanimous. So I think that is all right.

Thank you, Dr. Soldin. I will see
you tomorrow, and you will be faced with some others
almost immediately.

MS. CRONK: Thank you, sir.

THE COMMISSIONER: You will make the
arrangements, will you, Miss Cronk?

MS. CRONK: I will, sir.

THE COMMISSIONER: All right. We
will rise until ten o'clock tomorrow.

---- Whereupon the Hearing adjourned until 10:00 a.m.,
Thursday, July 7th, 1983.

